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Characteristics and research waste of randomized controlled trials in melanoma

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Abstract

Background Numerous large-scale randomized controlled trials (RCTs) have propelled melanoma treatment strategies. Research waste presents a significant challenge in translating the outcomes of RCTs into clinical practice. Currently, research waste has not been reported in melanoma-related RCTs.

Objectives To determine research waste in RCTs for melanoma.

Methods In January 2024, we searched ClinicalTrials.gov for phase III and phase IV RCTs registered from January 2000 to December 2023, using 'melanoma' as the keyword. We recorded the information listed on the website and searched PubMed and Scopus for the publication and citation status of the RCTs. A completed RCT requires at least 47 months of preparation time for publication; hence, RCTs completed after December 2019 but not yet published were excluded from the analysis of publication status.

Results In total, 165 RCTs were included in the analysis. Melanoma RCTs primarily studied pharmacological interventions, with the registrations for immunotherapy increasing annually. In the analysis of research waste, 103 RCTs were included, of which 41 (41 of 103, 39.8%) were unpublished. Of the 62 published RCTs, 19 (19 of 62, 31%) reported insufficiently, and 19 had avoidable design flaws (19 of 62, 31%). Ultimately, 64 RCTs (64 of 103, 62.1%) were judged to have research waste. Registration after 2010, conducting studies in multiple countries, using multiple drug interventions, and having survival as the primary outcome were independent protective factors against research waste. Thirty-four RCTs (34 of 62, 55%) were cited by guidelines, and 21 RCTs (21 of 62, 34%) reused their prospective data.

Conclusions We describe the characteristics of phase III and phase IV RCTs related to melanoma conducted over the past 2 decades. We identified a substantial degree of research waste. The protective factors against research waste revealed in this study can provide references for the rational and efficient conduct of new RCTs in the future.

What is already known about this topic?

- Currently, a vast number of randomized controlled trials (RCTs) have been conducted on melanomas.
- There has been no study analysing the situation of research waste in melanoma-related RCTs.

What does this study add?

- This study is the first to describe the changes in the characteristics of melanoma-related RCTs globally over the past 20 years and has identified a high burden of research waste in this field.
- Registration after 2010, conducting studies in multiple countries, using multiple drug interventions, and having survival rates as the primary outcome were independent protective factors against research waste.

Melanoma is the most aggressive form of skin cancer. Epidemiological research has indicated a significant and ongoing increase in the incidence of melanoma over the past 5 decades.[1] According to the World Health Organization, the rate of increase in cases of melanoma surpasses that of any other form of cancer.[2] A large number of randomized controlled trials (RCTs) have been conducted to explore and compare newly emerging, more effective therapeutic methods for melanoma. Over the past 20 years, the outcomes of these RCTs have significantly improved the treatment and

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prognosis for melanoma. The extensive exploration of new therapies through large cohorts has also greatly enhanced the overall survival.[3,4]

Although RCTs offer high-level evidence, research waste is an issue that cannot be ignored. Wasted RCTs consume medical resources and elevate the risk to enrolled patients. Lu *et al.* discovered that 86.9% of gastric cancer RCTs exhibited research waste.[5] Research waste can arise from multiple causes. For example, if the results of RCTs are not published, the resources invested in them become useless for improving clinical treatments. Secondly, avoidable design flaws can lead to research waste, just as improper implementation of randomization or blinding procedures may decrease the credibility of the conclusions. Lastly, inadequate reporting can affect the reproducibility of RCTs, thereby leading to research waste. Research waste may also result in the conclusions of RCTs not being adopted by guidelines.[6]

Currently, the extent of research waste in melanoma RCTs remains unclear. With the rising incidence of drug-resistant melanoma, there is a crucial need to conduct more RCTs to develop new therapeutic strategies.[7] Minimizing research waste is indispensable for ensuring that conclusions can guide clinical therapy appropriately, safely and efficiently. This study aims to describe the characteristics and research waste in melanoma RCTs over the past 20 years, exploring associated risk factors and areas for improvement.

Materials and methods

Design and data

This study followed the STROCSS criteria (Table S1; see Supporting Information).[8] The data used in this study were extracted from ClinicalTrials.gov, a public online registry of trials. We searched the ClinicalTrials.gov database using the keyword 'melanoma' within a single day (1 January 2024). Eligible RCTs were phase III or phase IV trials conducted from 1 January 2000 to 31 December 2023. Nonrandomized trials, trials other than phase III or phase IV, and trials unrelated to melanoma were excluded.

The recorded characteristics included registration date, intervention, the country of the principal investigator and other details. If an RCT was conducted across multiple healthcare institutions, it was classified as multicentric. If RCTs were carried out in multiple countries, they were defined as multinational. Funding sources were categorized into two groups: (i) none or departmental finding, and (ii) funding from industry or external sources.

To better illustrate the evolution of intervention methods, we divided them into five categories: (i) radiotherapy and chemotherapy, (ii) targeted therapy, (iii) immunotherapy, (iv) surgery and (v) others. The primary outcome measures were divided into two groups: (i) those with survival as the outcome (including overall survival, progression-free survival, recurrence-free survival and metastasis-free survival), and (ii) outcomes not related to survival.

We predetermined that RCTs with sample sizes falling below the lower quartile (25%) would be classified as small-sample RCTs.[5] This study was not prospectively registered because it is a retrospective analysis based on the data of previously registered clinical trials, rather than being a clinical trial itself or generating original clinical data directly.

Publications

We conducted searches in PubMed and Scopus using the National Clinical Trial (NCT) number, the names of the principal investigators, and keywords related to the interventions to check and confirm the publication status. If no corresponding manuscripts were found in PubMed and Scopus, we contacted the principal investigators to further enquire about the publication status. In the absence of a response, the RCT was considered unpublished by default. A study was recognized as published when a complete manuscript, accessible either online or in print, was found in a peer-reviewed journal.

The search was conducted on 1 January 2024. Chapman *et al.* stated that a completed RCT should have ≥ 47 months of preparation time for publication.[6] Therefore, in our analysis of publication status, we did not include RCTs completed after December 2019 but not yet published. The completed time is determined based on the study completion date displayed on the ClinicalTrials.gov website.

Evaluation of adequate reporting

The evaluation of adequate reporting for each manuscript was conducted in accordance with the CONSORT reporting guideline. According to the CONSORT standards, manuscripts involving pharmacological interventions included 37 items, while those involving nonpharmacological interventions comprised 40 items.[9,10] If the item is met, the total score is increased by 1 point. Two independent researchers scored the manuscripts based on the CONSORT 2010 checklist. Discrepancies were resolved through consensus discussions after every three manuscripts assessed.

Given the extensive number of items in the CONSORT reporting guideline and that each item was attributed a point, inter-rater agreement was not recorded. The complete manuscript and supplementary materials were examined to assess the availability of a protocol. As described before, manuscripts that fulfilled 75% of the criteria (i.e. 28 of 37 pharmacological items or 30 of 40 nonpharmacological items) were deemed to have sufficient reporting.[6]

Design flaw evaluation

Utilizing the Cochrane tool, two independent reviewers evaluated anonymized manuscripts to appraise the risk of bias. Each type of bias was classified as either low, unclear or high risk.[11] Any disagreements were resolved by consensus after the evaluation of every three papers. In the statistical analysis, unclear bias was treated as high risk due to the potential impact of vague methodological descriptions on the credibility of an RCT.

Furthermore, the existence of a pertinent systematic review, or an explanation for its absence in novel settings, was examined. This needed to be referenced in the complete manuscript and be considered capable of informing the necessity of conducting the RCT. Studies exhibiting any of the aforementioned biases or not citing a relevant

systematic review were regarded as having an avoidable design flaw.

References to papers in guidelines and reuse of prospective data

For each published RCT, we initially searched articles citing the RCT within the Google Scholar database. Following this, two independent investigators meticulously examined each article referencing the RCT to identify the presence of practice guidelines. Additionally, we evaluated the reuse of prospective data for subsequent post hoc analyses (i.e. analysing data from the RCT for outcomes not originally designated as primary or secondary endpoints). It was presumed that such post hoc analyses invariably referenced the original RCT.

Statistics

Categorical variables are displayed as counts and proportions, whereas continuous variables are represented as medians and interquartile ranges. Comparisons of categorical variables between groups were performed using the χ^2 test or Fisher's exact test. Both univariate and multivariate logistic regression analyses were employed to identify independent risk factors linked to research waste. Factors demonstrating a P-value < 0.05 in the univariate analysis were then considered for inclusion in the multivariate analysis. Statistical evaluations were conducted using SPSS version 26.0 (IBM, Armonk, NY, USA) and R version 4.0.6 (R Foundation, Vienna, Austria). A P-value < 0.05 was considered to indicate statistical significance, and all analyses were two sided.

Results

Based on the inclusion and exclusion criteria, in total, 165 RCTs were included in the analysis (Figure 1a). The first quartile of the recruitment number is 151 participants; therefore, we used 150 as the cutoff value to assess the impact of differences in the number of participants. The majority of RCTs were pharmacological (87.3%), multicentre (81.2%) and multinational (62.4%). Europe and North America were the primary regions for carrying out melanoma RCTs (Figure S1; see Supporting Information), with the majority of RCTs being conducted in high-income countries within these regions (92.7%). One hundred RCTs (60.6%) received funding from external sources or manufacturers (Table 1).

The number of RCTs registered for different interventions over the past 2 decades reflects the trend in treatment development. Traditional radiotherapy and surgical treatments showed a gradual decline. Targeted therapy registrations gradually increased until 2015, after which they began to level off. In contrast, registrations for immunotherapy have continuously increased (Figure 1b).

Publication status

In this section, we excluded RCTs that ended after December 2019 and had not yet been published ($n = 62$) (Table S2; see Supporting Information). Among the remaining 103 RCTs, 62 (60.2%) were published in peer-reviewed journals and were available for full-text review. Of these, 56 (90%) involved pharmacological interventions, while only 6 (10%) included nonpharmacological interventions. Compared with unpublished RCTs, those published were more likely to be multinational ($P = 0.009$), to investigate multiple drugs ($P = 0.005$), to have survival as the primary outcome ($P < 0.001$), to receive external funding ($P = 0.02$) and to have a sample size ≥ 150 ($P = 0.002$) (Table S2). Additionally, in multivariate analysis, having survival as the primary outcome ($P = 0.006$) was an independent protective factor against RCTs remaining unpublished (Table S3; see Supporting Information).

Adequacy of reporting

Table S4 (see Supporting Information) shows the scores obtained for the 62 published RCTs based on the CONSORT checklist. In the RCTs with pharmacological interventions

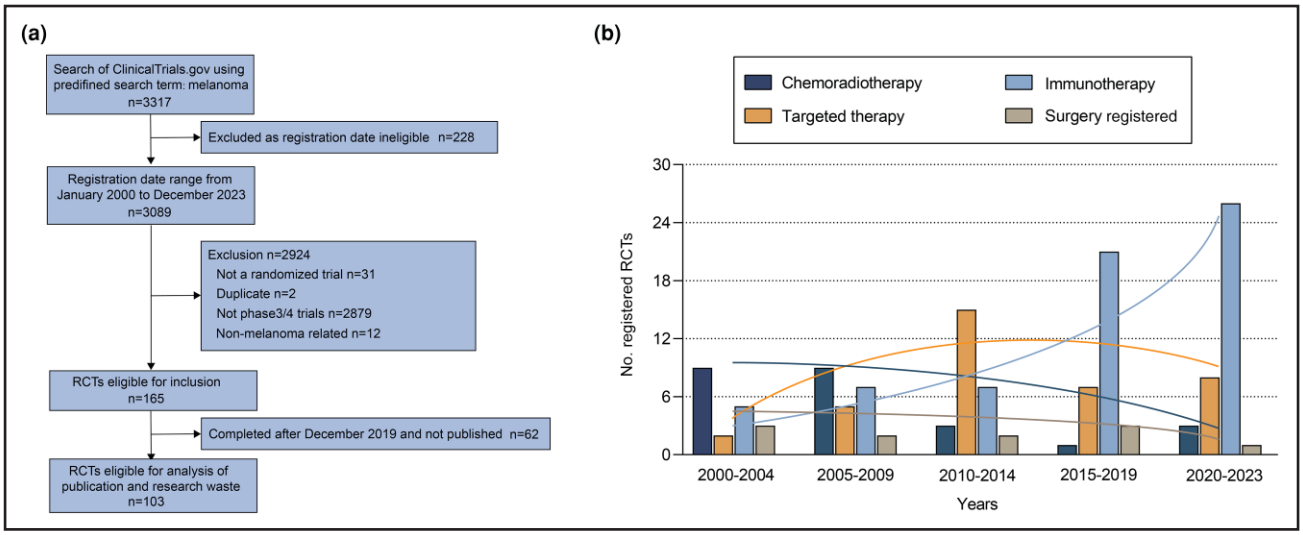

Figure 1 (a) Flowchart of study identification. (b) Number of conducted randomized controlled trials (RCTs) by category.

Table 1 Characteristics of all included randomized controlled trials

	***N* = 165**
Enrolment time (months), median (IQR)	46 (26–82)
Registration time	
2000–2004	22 (13.3)
2005–2009	27 (16.4)
2010–2014	34 (20.6)
2015–2019	40 (24.2)
2020–2023	42 (25.5)
Number of centres	
Monocentric	31 (18.8)
Multicentric	134 (81.2)
Number of countries	
Single country	62 (37.6)
Multinational	103 (62.4)
Intervention	
Pharmacological	144 (87.3)
Nonpharmacological	21 (12.7)
Intervention	
Chemoradiotherapy	25 (15.1)
Targeted therapy	37 (22.4)
Immunotherapy	66 (40.0)
Surgery related	11 (6.7)
Other	26 (15.8)
Primary purpose	
Treatment	156 (94.5)
Other	9 (5.5)
Study design	
Parallel	156 (94.5)
Other	9 (5.5)
Number of arms	
2	134 (81.2)
3	22 (13.3)
≥ 4	9 (5.5)
Blinding	
None/open label	98 (59.4)
Single	5 (3.0)
Double	27 (16.4)
Triple	11 (6.7)
Quadruple	24 (14.5)
Economic region of principal investigator	
High-income country	153 (92.7)
Middle-income country	12 (7.3)
Recruitment region	
Europe	60 (36.4)
Asia	9 (5.5)
North America	89 (53.9)
South America	1 (0.6)
Oceania	6 (3.6)
Primary outcome measure	
Overall survival	41 (24.9)
Progression-free survival	37 (22.4)
Recurrence-free survival	26 (15.8)
Metastasis-free survival	7 (4.2)
Other	54 (32.7)
Funding type	
None/departmental	65 (39.4)
Industry/other	100 (60.6)
No. of participant	
< 150	40 (24.2)
≥ 150	125 (75.8)

The data are presented as *n* (%) unless stated otherwise. IQR, interquartile range.

(*n*=56), notable reporting deficiencies included access to the complete trial protocol (79%), details of randomization (77%) and implementation of random sequence allocation (68%). For RCTs of nonpharmacological interventions (*n*=6), prominent reporting deficiencies were in random sequence allocation (100%) and the presentation of the complete trial protocol (100%). Overall, 43 (69%) were judged to have adequate reporting.

Compared with RCTs with insufficient reporting, those with adequate reporting were more likely to have been registered after 2010 ($P=0.03$), to be multicentric ($P=0.001$), to be multinational ($P<0.001$), to involve multiple pharmacological interventions ($P<0.001$), to receive external funding ($P=0.02$) and to have a recruitment number ≥ 150 ($P<0.001$) (Table S5; see Supporting Information). Moreover, being multinational ($P=0.001$) and studying more than two drugs ($P=0.005$) were identified as independent risk factors for adequate reporting in RCTs (Table S6; see Supporting Information).

Design flaws

Among the 62 published RCTs, 12 (19%) lacked references to relevant systematic literature reviews. Additionally, 14 RCTs (23%) exhibited at least 1 feature indicating a high or unclear risk of bias. Figure 2 shows that the most common biases were selective reporting (26%), blinding of outcome assessors (21%) and concealed random sequence allocation (21%). When considering both factors simultaneously, 19 RCTs (31%) were identified as having avoidable design flaws. These RCTs were more likely to be registered earlier ($P=0.001$), to be monocentric ($P=0.001$), to be conducted in a single country ($P<0.001$), to involve a single drug or nonpharmacological interventions ($P=0.002$), to not have survival as the primary outcome ($P=0.03$) and to have a sample size < 150 ($P<0.001$) (Table S7; see Supporting Information). Regression analysis revealed that registration after 2010 was an independent protective factor ($P=0.008$) against the occurrence of design flaws (Table S8; see Supporting Information).

Research waste

When combining the statuses of 'publication status', 'adequate reporting' and 'avoidable design flaws', 64 of the 103 RCTs (62.1%) exhibited at least 1 form of research waste. These RCTs were more likely to have been registered before 2010 ($P=0.001$), to be designed as single-centre studies ($P=0.002$), to be conducted in a single country ($P<0.001$), to have no external funding ($P=0.001$), to utilize nonpharmacological or single drug interventions ($P<0.001$), to not have survival as the primary outcomes ($P<0.001$) and to have a sample size < 150 participants ($P<0.001$) (Table 2).

Multivariate analysis indicated that registration after 2010 ($P=0.002$), conducting studies in multiple countries ($P=0.003$), using two or more drug interventions ($P=0.004$) and having survival as the outcome measure ($P=0.01$) were independent protective factors against research waste (Table S9; see Supporting Information).

Referencing in guidelines and reuse of prospective data

Of the 62 published RCTs, 34 (55%) have been cited by guidelines. These RCTs were predominantly multicentre ($P=0.02$) or multinational ($P=0.005$), had a recruitment size ≥ 150 participants ($P=0.008$) and had absence

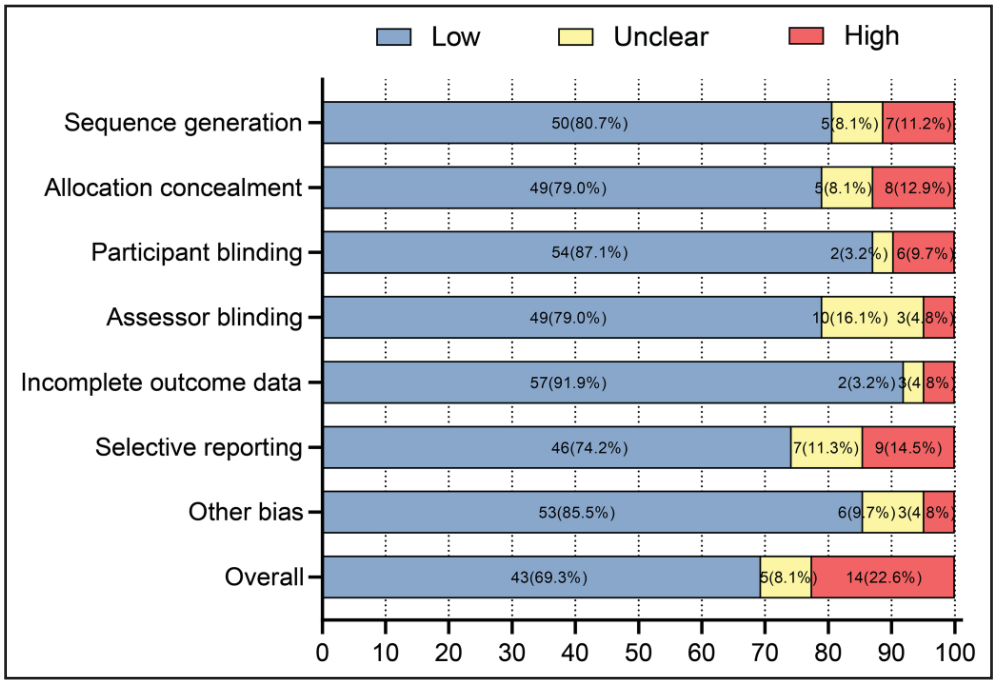

Figure 2 Risk-of-bias assessment. Results for individual components of the Cochrane tool for assessing risk of bias are shown. Items with an unclear risk of bias were considered together with high-risk items in the analyses.

of research waste ($P=0.001$) (Tables S10 and S11; see Supporting Information). Furthermore, 21 RCTs (34%) reused their prospective data. Regression analysis indicated that registration after 2010 ($P=0.03$) and conducting studies in multiple countries ($P=0.04$) were independent risk factors for the reuse of prospective data (Tables S12 and S13; see Supporting Information).

Discussion

To our knowledge, our study describes for the first time the characteristics of 165 phase III and phase IV RCTs related to melanoma over the past 2 decades and has identified a considerable extent of research waste (62.1%). Of the 103 RCTs completed before December 2019, 62 have been published. Furthermore, 43 RCTs reported adequately, while 19 RCTs had avoidable design flaws. Further analysis suggests that registration after 2010, conducting studies in multiple countries, using two or more drug interventions, and having survival as the outcome measure may be associated with reducing research waste. However, these factors should not be directly equated with research waste.

The early-phase, single-centre, single-intervention, small RCTs serve as a basis for future larger-scale RCTs, allowing researchers to quickly gain preliminary insights into existing evidence. Therefore, priority should be given to quality improvement strategies that enhance the basic availability of resources, such as statistical analysis and trial management.[12] Encouraging cooperation among multiple centres or countries is meaningful, and it is preferable in order to reduce redundant research and minimize unnecessary financial expenses.

In the field of cancer research, the phenomenon of research waste is widespread, posing a significant challenge to the efficient use of resources. A study by Lu *et al.* showed that up to 86.9% of RCTs related to gastric cancer exhibited research waste,[5] while Lin *et al.* found that this proportion stands at 82.1% for RCTs related to ovarian cancer.[13] However, our understanding of research waste in other cancers or dermatological conditions remains relatively limited.

Previous studies have also identified that implementing blinding and appropriate sample-size planning are crucial to avoiding research waste.[5,13] In our analysis of melanoma, we found a somewhat different scenario: RCTs involving multiple countries or various drug interventions, and with survival as the primary outcome seemed more inclined to reduce research waste. This might suggest that specific strategies used in the design and implementation of studies, such as choosing meaningful clinical outcomes and ensuring the multicentric nature of research, could help enhance research efficiency and thus reduce waste. This provides important references for other cancer or dermatological disease research. Comparing our findings with research in other cancers highlights the unique challenges and opportunities present in cancer research and underscores the importance of further exploring how greater efficiency and effectiveness can be achieved in all cancer research.

When testing new therapeutic strategies, RCTs are commonly utilized as a means to reduce bias. The necessity for conducting certain RCTs to advance treatment developments depends on the severity of the cancer's impact. However, previous research has indicated a mismatch between the disease burden and corresponding funding.[14,15] Scholars have suggested that a comprehensive review of existing research foundations and conclusions should precede the initiation of new studies.[16] New trials should only be embarked upon when current data inadequately address the challenges.

Table 2 Characteristics of randomized controlled trials according to the presence of research waste

	Research waste, *n* (%)		
	Present (*n* = 64)	**Absent (*n* = 39)**	***P*-value**
Registration time			0.001
2000–2009	38 (59)	9 (23)	
After 2010	26 (41)	30 (77)	
Number of centres			0.002
Monocentric	19 (30)	1 (3)	
Multicentric	45 (70)	38 (97)	
Number of countries			< 0.001
Single country	34 (53)	2 (5)	
Multinational	30 (47)	37 (95)	
Intervention			0.12
Pharmacological	53 (83)	37 (95)	
Not pharmacological	11 (17)	2 (5)	
Intervention			< 0.001
Single medication or nonpharmacological	37 (58)	5 (13)	
Multiple medications	27 (42)	34 (87)	
Intervention			0.48
Immunotherapy	19 (30)	15 (38)	
Not immunotherapy	45 (70)	24 (62)	
Intervention			0.15
Targeted therapy	12 (19)	13 (33)	
Not targeted therapy	52 (81)	26 (67)	
Primary purpose			0.08
Treatment	58 (91)	39 (100)	
Other	6 (9)	0 (0)	
Study design			0.71
Parallel	59 (92)	37 (95)	
Other	5 (8)	2 (5)	
Number of arms			0.37
2	55 (86)	30 (77)	
≥ 3	9 (14)	9 (23)	
Blinding			0.14
None/open label	42 (66)	19 (49)	
≥ 1	22 (34)	20 (51)	
Economic region of PI			> 0.99
High-income country	61 (95)	38 (97)	
Middle-income country	3 (5)	1 (3)	
Region of PI			0.64
Europe	22 (34)	16 (41)	
Not Europe	42 (66)	23 (59)	
Region of PI			> 0.99
North America	36 (56)	22 (56)	
Not North America	28 (44)	17 (44)	
Primary outcome			< 0.001
Survival	34 (53)	35 (90)	
Not survival	30 (47)	4 (10)	
Funding type			0.001
None/departmental	33 (52)	7 (18)	
Industry/other	31 (48)	32 (82)	
Number of participants			< 0.001
< 150	27 (42)	0 (0)	
≥ 150	37 (58)	39 (100)	

PI, principal investigator.

We have described the features of melanoma RCTs over the past 2 decades, noting an annual increase in their registration numbers. Therefore, we should be vigilant about the occurrence of research waste. With the advent of precision medicine, we can predict that treatments targeting molecular mechanisms will continue to be a primary area of future research. We have also observed that both the proportion and the number of immunotherapy studies are increasing year by year. Immunotherapy, by leveraging the body's own immune system to combat cancer, presents a paradigm shift away from traditional treatments and towards more personalized and targeted approaches.[17] While this may play a pivotal role in advancing future treatments for melanoma, it is crucial to ensure that RCTs are designed in harmony with up-to-date discoveries and forward-moving trends to reduce unnecessary research waste.

We compared the publication status of completed melanoma RCTs in Europe, North America and other regions (Tables S2 and S3). Our analysis did not reveal any statistical differences in publications across these regions. This finding suggests that stringent regulations and legislation, while crucial for ensuring the ethical conduct of trials and the reporting of results, may not directly influence the publication of RCTs in melanoma. However, it is important to note

that the lack of statistical analysis for other regions due to insufficient sample sizes might limit the generalizability of this conclusion. This outcome underscores the complexity of factors that influence the publication of clinical trials and suggests that additional mechanisms beyond regulation and legislation might be needed to enhance the transparency and dissemination of research findings in the scientific community.

Several limitations to our study deserve deeper investigation. Firstly, the conditions for assessing research waste are not confined to the three items described in this paper, with different studies having varying definitions. Although our analysis did not directly encounter instances of 'me too trials' or covert duplicate publications, these forms of research waste present significant challenges to the scientific community. Their potential presence in fields beyond our current focus highlights the necessity for vigilant screening and assessment protocols in RCT research.

Secondly, some metrics were assessed manually, which might lead to inaccuracies in measurements. We employed two independent investigators to analyse the RCTs and resolved disagreements through discussion, aiming to minimize assessment errors as much as possible. Lastly, although ClinicalTrials.gov is the most commonly used clinical trial registry, some studies are only registered on national websites and they were not included in our analysis.[18] Also, our search did not extend to other sources of result sharing, such as trial registration sites that mandate the posting of results within a specific timeframe regardless of journal publication, or results presented at meetings. Future studies could benefit from incorporating these additional sources to provide a more holistic view of the state of research in the field.

Conclusions

We have identified that the melanoma RCTs conducted over the past 2 decades have exhibited a certain degree of research waste. Registration after 2010, multinational conduction, comparing two or more pharmacological interventions, and having survival as the outcome measure were found to be independent protective factors against research waste. There are areas for improvement in the design, implementation, outcome presentation and reuse of prospective data in melanoma RCTs. The findings of this study offer insights for the future development of melanoma RCTs to reduce research waste.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The datasets generated and/or analysed during the current study are available at ClinicalTrials.gov, a public registry of trials.

Ethics statement

The ethics board of Shanghai Ninth Hospital, Shanghai Jiao Tong University School of Medicine concluded that this cross-sectional analysis, being a scrutiny of registered RCTs, did not necessitate ethical approval for research or the need for informed consent from participants.

Patient consent

Not applicable.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

References

1 Linos E, Swetter SM, Cockburn *et al.* Increasing burden of melanoma in the United States. *J Invest Dermatol* 2009; **129**: 1666–74.
2 Lens MB, Dawes M. Global perspectives of contemporary epidemiological trends of cutaneous malignant melanoma. *Br J Dermatol* 2004; **150**:179–85.
3 Larkin J, Chiarion-Sileni V, Gonzalez R *et al.* Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2019; **381**:1535–46.
4 DeSantis CE, Lin CC, Mariotto AB *et al.* Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin* 2014; **64**:252–71.
5 Lu J, Xu BB, Shen LL *et al.* Characteristics and research waste among randomized clinical trials in gastric cancer. *JAMA Netw Open* 2021; **4**:e2124760.
6 Chapman SJ, Aldaffaa M, Downey CL, Jayne DG. Research waste in surgical randomized controlled trials. *Br J Surg* 2019; **106**:1464–71.
7 Ferretti LP, Böhi F, Pedrioli DML *et al.* Combinatorial treatment with PARP and MAPK inhibitors overcomes phenotype switch-driven drug resistance in advanced melanoma. *Cancer Res* 2023; **83**:3974–88.
8 Mathew G, Agha R, Albrecht J *et al.* STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case–control studies in surgery. *Int J Surg* 2021; **96**:106165.
9 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **340**:c332.
10 Boutron I, Moher D, Altman DG *et al.* Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. *Ann Intern Med* 2008; **148**:295–309.
11 Higgins JPT, Altman DG, Gøtzsche PC *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**:d5928.

12 Zarin DA, Goodman SN, Kimmelman J. Harms from uninformative clinical trials. *JAMA* 2019; **322**:813–14.
13 Lin L, Tang Y, Yang L *et al*. Research waste among randomized controlled trials in ovarian cancer: a cross-sectional study. *Eur J Surg Oncol* 2024; **50**:108437.
14 Liberati A. Need to realign patient-oriented and commercial and academic research. *Lancet* 2011; **378**:1777–8.
15 Corner J, Wright D, Hopkinson J *et al*. The research priorities of patients attending UK cancer treatment centres: findings from a modified nominal group study. *Br J Cancer* 2007; **96**:875–81.
16 Chalmers I, Bracken MB, Djulbegovic B *et al*. How to increase value and reduce waste when research priorities are set. *Lancet* 2014; **383**:156–65.
17 Kundu M, Butti R, Panda VK *et al*. Modulation of the tumor microenvironment and mechanism of immunotherapy-based drug resistance in breast cancer. *Mol Cancer* 2024; **23**:92.
18 Tse T, Fain KM, Zarin DA. How to avoid common problems when using ClinicalTrials.gov in research: 10 issues to consider. *BMJ* 2018; **361**:k1452.