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A systematic review of ethnic minority participation in randomised controlled trials of systemic therapies for gynecological cancers

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HIGHLIGHTS

- 17,041 patients participated in 26 randomised controlled trials of systemic therapies for gynecological cancers.
- Ethnic minority patients formed small proportions of randomised controlled trial participants on the global scale.
- 79.8% of patients were "Caucasian", 9.1% "East Asian", 3.7% "Black/African American" and 7.5% of other ethnicity.
- Research sites were concentrated in North America and Europe, with 93% of sites located in these regions.
- Only 7% of research sites were located in regions other than North America or Europe.

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ABSTRACT

Objective. Randomised controlled trials (RCTs) must include ethnic minority patients to produce generalisable findings and ensure health equity as cancer incidence rises globally. This systematic review examines participation of ethnic minorities in RCTs of licensed systemic anti-cancer therapies (SACT) for gynecological cancers, defining the research population and distribution of research sites to identify disparities in participation on the global scale.

Methods. A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Phase II and III RCTs of licensed therapies for gynecological cancers published 01/11/2012–01/11/2022 that reported patient race/ethnicity were included. Extracted data included race/ethnicity and research site location. RCT populations were aggregated and participation of groups compared. Global distribution of research sites was described.

Results. 26 RCTs met inclusion criteria of 351 publications included in full-text screening, representing 17,041 patients. 79.8% were "Caucasian", 9.1% "East Asian", 3.7% "Black/African American" and 6.1% "Other, Unknown, Not Reported". "Caucasian" patients participated at higher rates than all other groups. Of 5,478 research sites, 80.1% were located in North America, 13.0% in Europe, 3.4% in East Asia, 1.3% in the Middle East, 1.3% in South America and 0.8% in Australasia.

Conclusions. Ethnic minorities formed smaller proportions of RCT cohorts compared to the general population. The majority of sites were located in North America and Europe, with few in other regions, limiting enrollment of South Asian, South-East Asian and African patients in particular. Efforts to recruit more ethnic minority patients should be made in North America and Europe. More sites in underserved regions would promote equitable access to RCTs and ensure findings are generalisable to diverse groups. This review assessed the global population enrolled in contemporary RCTs for novel therapies now routinely given for gynecological cancers, adding novel understanding of the global distribution of research sites.

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Contents

1. Introduction

1.1. Rationale

Participants in cancer randomised controlled trials (RCTs) represent <5% of the patient population, often differing from real-world patient populations in terms of fitness, age, socioeconomic status and other factors [1,2]. The generalisability of findings to real-world populations is also limited by the historically low participation of ethnic minority patients in clinical trials [3,4]. Differing responses to systemic anti-cancer therapy (SACT) relative to ethnicity have been observed in many cancer types, with emerging evidence suggesting genetic differences between ethnic groups can affect toxicity burdens and treatment outcomes [5–7].

In ovarian cancer, pharmacogenomic differences in response to SACT have been observed in patients of different ethnicities [8]. For example, superior tolerability of dose-dense (two-weekly) paclitaxel was observed in European patients compared to Japanese patients, who were more likely to terminate treatment early due to unacceptable toxicity [9]. Despite higher toxicity burden, the Japanese cohort showed superior overall survival outcomes. Another study, conducted in Singaporean and Australian sites, showed that Asian patients experienced a higher incidence of febrile neutropaenia when treated with docetaxel and carboplatin compared to the Australian cohort, and that this was related to slower metabolism and clearance of docetaxel [10]. These observations highlight disparities in treatment effects between patients of different ethnicity receiving SACT, warranting further investigation.

1.2. Objectives

This systematic review examines the global participation of ethnic minority patients in RCTs of SACT for newly-diagnosed and recurrent gynecological cancers over a ten-year period, providing a novel assessment of the study population that participated in successful RCTs for novel therapies now routinely used in these cancers. This is of clinical importance as the treatment landscape for these cancers has changed significantly over the previous decade. A contemporaneous analysis of the patient population that participated in these RCTs is useful both in determining the equity of access to research, and to inform future observational studies into disparities between subgroups. Describing this patient cohort allows for a specific analysis of the groups represented in trials that have directly led to drug licensing, and can inform future research into the emerging field of treatment disparities within subgroups of gynecological cancer patients. This systematic review also adds knowledge to the field of equity in clinical research through the assessment and description of the global distribution of research sites, relating the concentration of sites in specific regions to disparity observed in RCT participation relative to patient ethnicity, and builds upon a previous review of ethnic minority participation in *Gynecologic Oncology Group* RCTs conducted in the period 1985-2013 by providing an updated assessment of representation of minority groups in a contemporary period where novel therapies have been introduced in gynecological cancers [11]. Whilst other authors have conducted large reviews of ethnic minority enrollment to RCTs more generally and across multiple disciplines [12,13], this review focuses on representation in contemporary gynecological cancer RCTs during a period where there have been significant changes in the systemic treatment landscape. The aim is to provide an up-to-date assessment of ethnic minority representation, both to assess the impact of policies aiming to improve representation and to future observational research into the emerging field of pharmacoequity and differences in systemic treatment effects in patients from diverse ethnic backgrounds.

2. Methods

This is a systematic review based on peer-reviewed academic publications of RCT results. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed for reporting of the methods and findings [14]. The review protocol was registered in the Prospero International Prospective Register of Systematic Reviews (CRD), ID CRD42022369370.

2.1. Eligibility criteria

Studies reporting enrollment by ethnicity, race or equivalent *and* investigating SACT licensed for use in newly-diagnosed or recurrent gynecological cancers (ovarian, endometrial, cervical, vaginal and vulvar) in any country at time of search were eligible. Studies of surgery,

radiotherapy or hormonal therapy alone were excluded. Non-randomised trials, case reports, pharmacokinetic, safety and dose-finding studies were excluded. Phase II and III RCTs only were included. Only studies in adults (18+) and in English language were included.

2.2. Information sources and search strategy

MEDLINE, Embase, ClinicalTrials.gov and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched on 10/11/2022 using MESH and keyword terms based on PRISMA guidelines. Publications of RCTs of SACT for gynecological cancers published between 10/11/2012 and 01/11/2022 were eligible. Full search strategy including MESH and keyword terms are provided in Supplementary Table 1. Database searches and screening were undertaken by one author (LS) and verified by another (UC) to ensure consistency in the screening process, as per standard practice for systematic reviews following PRISMA guidelines [15]. Articles were sorted into "include", "exclude" or "unsure" categories, and were included in the review by consensus decision when designated as "unsure". Where texts were unavailable to read, authors were contacted.

2.3. Data extraction process

Data of interest included number of patients recruited by "race" (defined by the American Sociological Association as "groups based on physical traits regarded as common among people of shared ancestry"), "ethnicity" (defined as "shared culture, such as language, ancestry, practices and beliefs") [16], or equivalent term, cancer type, cohort size, descriptions and size of interventional, active comparator/placebo arms, publication date and locations of research sites by country. Patient numbers by ethnicity and race, as reported in the baseline characteristics table or supplementary materials, were extracted independently by two authors (LS and UC) to ensure accuracy, as is standard practice for systematic reviews. Race/ethnicity terms were grouped where applicable (described further in results section). Where patient ethnicity was described as "not reported", data were extracted as the extent of unreported patient ethnicity in trials was also considered an outcome for the review. Discrepancies in data extraction were discussed between authors and agreed by consensus. Authors were not contacted where ethnicity data were missing, as reporting of participant ethnicity was an outcome for this review. Data are not planned for public dissemination.

2.4. Data synthesis and statistical analysis

Percentage enrollment was calculated for each ethnic group. Overall enrollment was compared between ethnic groups, trial phase and disease indication. Enrollment of minority groups was compared to incidence of gynecological cancers by ethnicity in US and UK populations. Wilcoxon signed-rank T-tests were used to assess differences in enrollment between groups. Data were extracted and tabulated in Microsoft Excel. Statistical analysis was conducted with RStudio v4.1.3 and p-values <0.05 were considered statistically significant. Percentage enrollment of each ethnic minority group was represented as forest plots and given in tables describing absolute counts of enrollment and research site locations by country.

2.5. Risk of bias assessments

Risk-of-bias assessments were conducted by author LS using Cochrane Risk-of-Bias Tool for Randomized Trials (RoB-2) [17]. As data extracted were enrollment by ethnicity and research site location, this was considered appropriate for this review. Risk of bias assessments were reported as traffic light plots for individual studies, and overall risk of bias was reported for all included RCTs.

3. Results

3.1. Article screening and description of included studies

26 individual RCTs met inclusion criteria and were included in the review. Of 13,293 articles identified through databases searches, 8,268 duplicates were removed and 4,674 articles excluded at the title and abstract screening stage. In full-text screening, of 351 articles, 325 exclusions were made: 239 articles (68%) did not report enrollment by ethnicity, 67 (19%) investigated a non-licensed therapy, nine (2.6%) were incomplete or reported interim results, and full-text was unavailable for four articles (1.1%). Six articles were excluded for reporting results from the same RCT in multiple publications. In cases where full-text articles were not available, authors were contacted but did not respond to requests for article sharing. Full details of exclusions are given as a flowchart in Fig. 1. Several studies which appear to meet inclusion criteria but were excluded due to the therapy not being licensed for use in a gynecological cancer at the time of review are cited (according to PRISMA checklist guidelines) [18–20].

20 studies were in ovarian cancer, four in cervical and two in endometrial. Eight RCTs studied PARP inhibitors, seven studied bevacizumab (alone or in combination with other SACT), nine studied chemotherapy alone, and two studied pembrolizumab. Table 1 gives summary characteristics of included studies.

3.2. Enrollment by ethnicity

In total, 17,041 patients participated in 26 RCTs. 79.8% of patients were "Caucasian (n=13,595), 9.1% "East Asian" (n=1,552), 3.7% "Black/African American" (n=630), 6.% "Other, Unknown, Not Reported or Missing" (n=1,031), 0.6% "Hispanic or Latino" (n=101), 0.5% "Asian/Unknown/Other" (n=87), 0.1% "American Indian or Alaska Native" (n=18), 0.1% "Native Hawaiian or Pacific Islander" (n=15) and 0.1% "Hispanic/Other/Unspecified" (n=12). Percentage enrollment of each ethnic group is shown as a forest plot in Fig. 2. Total enrollment to RCTs by grouped ethnicity are shown in Table 2, and enrollment figures as provided in publications are shown in Supplementary Table 2. By disease indication, 73.5% of patients participated in ovarian cancer RCTS (n=12,529), 20.2% in endometrial RCTs (n=3,443) and 6.3% in cervical (n=1,069). Enrollment by ethnicity for RCTs in each disease indication is shown in Supplementary Fig. 1.

RCT participation of each group was compared to US incidence counts for ovarian, cervical and endometrial cancer respectively as these data were available, with comparisons shown in Fig. 3. "Caucasian" and "Asian/Pacific Islander" groups showed over-representation in RCTs compared to incidence in the general population. "Black/African American" and patients classified as "Other" enrolled at rates lower than incidence in the general population. Reference populations for each group were based on counts of new cases in the US for each ethnic group in 2020 [21]. Comparisons are also made to the UK patient population in Supplementary Fig. 2.

The majority of patients participated in phase III RCTs, where 93.0% (15,845) patients were recruited compared to 7% (1196) to phase II. "Caucasian" patients participated at higher rates in phase II studies, forming 83.4% of cohorts in phase II studies and 79.5% of patients in phase III ($p<0.01$). "Black/African American" patients participated at greater rates in Phase III studies, forming 5.8% of patient cohorts in phase II compared to 2.4% in phase III RCTs. Wilcoxon t-tests were performed to test for significant differences in mean enrollment between ethnic groups with values given in Supplementary Table 3. For all other groups, no significant differences were observed between percentage enrollment by trial phase ($p>0.05$ in all cases). Enrollment by trial phase is shown in Supplementary Fig. 3 and significance values of statistical tests in Supplementary Table 4.

Grouping of ethnicity terms was necessary to enable appropriate comparisons of enrollment. Groupings were made as follows: "East

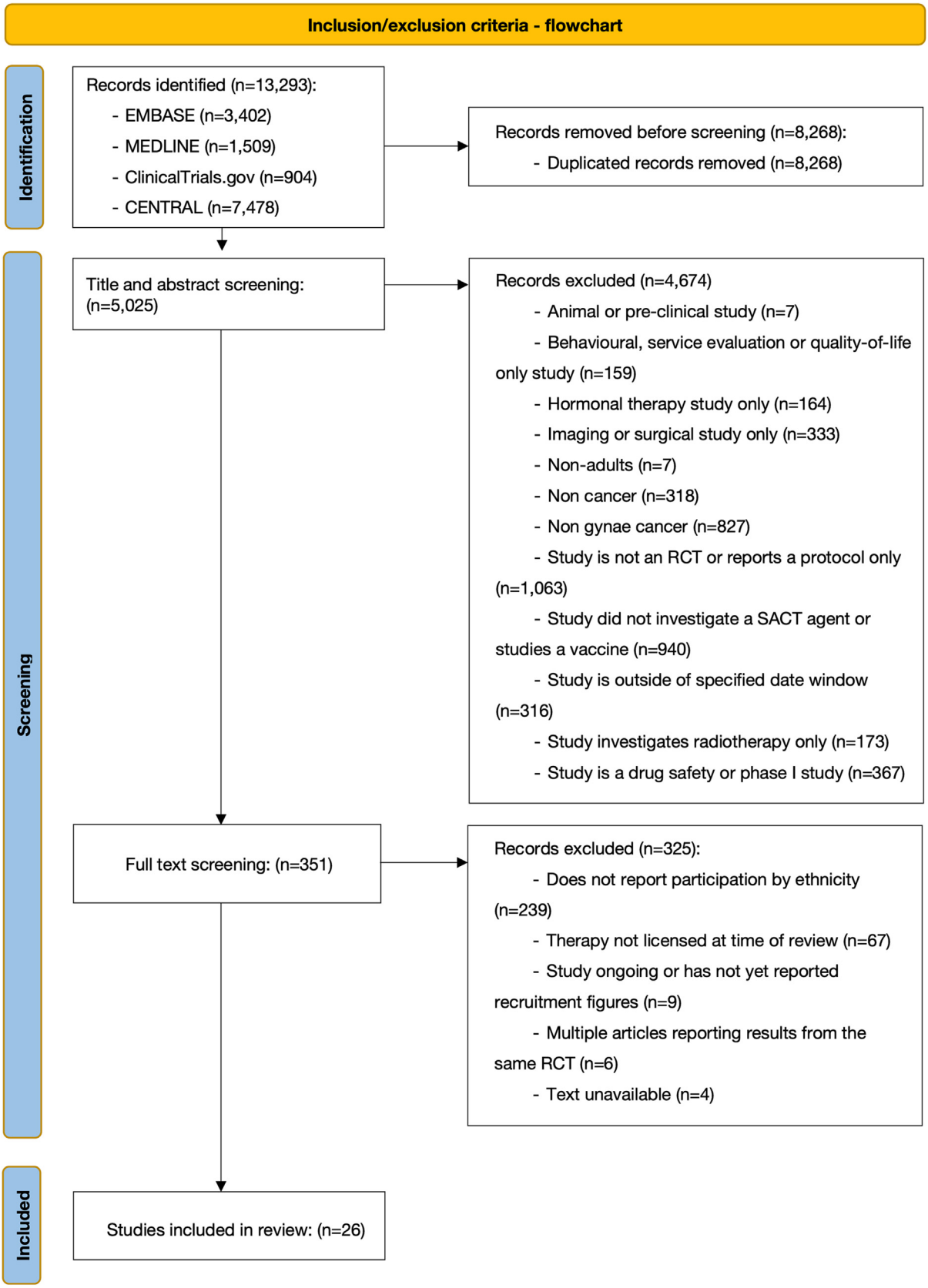

Fig. 1. PRISMA flowchart of exclusion criteria

Table 1
Summary of systematic review publications with description of disease indication, investigative therapies, participating sites, study population and risk of bias assessment.

Study	Publication title	Trial acronym	Disease indication	Trial registration number	Experimental agent(s)	Comparator agent(s)	Number of sites	Countries	Total study population (N)	Risk of bias assessment
Walker et al. (2019)	Randomized Trial of Intravenous Versus Intraperitoneal Chemotherapy Plus Bevacizumab in Advanced Ovarian Carcinoma: An NRG Oncology/Gynecologic Oncology Group Study [39]	GOG-0252	Ovarian	NCT00951496	IP Carboplatin or IP Cisplatin	IV Carboplatin	503	USA	1,560	Low
Moore et al. (2021	Atezolizumab, Bevacizumab, and Chemotherapy for Newly Diagnosed Stage III or IV Ovarian Cancer: Placebo-Controlled Randomized Phase III Trial (IMagyn050/GOG 3015/ENGOT-OV39) [40]	iMagyn050/GOG3015/ENGOT-OV39	Ovarian	NCT03038100	Atezolizumab, bevacizumab, carboplatin + paclitaxel	Placebo, bevacizumab, carboplatin + paclitaxel	268	Australia, Austria, Brazil, Belgium, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Israel, Italy, Japan, South Korea, Norway, Poland, Russia, Spain, Sweden, Turkey, USA	1,301	Low
Tewari et al. (2019)	Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer [41]	GOG-2018	Ovarian	NCT00262847	Arm I: Bevacizumab concurrent + maintenance Arm II: Bevacizumab - concurrent	Carboplatin + paclitaxel	632	Canada, Japan, South Korea, USA	1,873	Low
Tewari et al. (2017)	Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240) [42]	GOG-240	Cervical	NCT00803062	Bevacizumab + chemotherapy	Chemotherapy	549	Spain, USA	452	Low
Ledermann et al. (2016)	Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial [43]	Study-19	Ovarian	NCT00753545	Olaparib	Placebo	74	Australia, Austria, Belgium, Canada, Czech Republic, Estonia, France, Germany, Israel, Netherlands, Poland, Romania, Russia, Spain, Ukraine, United Kingdom, USA	265	Low
Provencher et al. (2018)	OV21/PETROC: a randomized Gynecologic Cancer Intergroup phase II study of intraperitoneal versus intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer [44]	OV21/PETROC	Ovarian	NCT00993655	Intraperitoneal chemotherapy (neoadjuvant)	Intravenous chemotherapy (neoadjuvant)	50	Canada, Spain, United Kingdom, USA	275	Low
Vergote et al. (2020)	A randomized phase III trial in patients with recurrent platinum sensitive ovarian cancer comparing efficacy and safety of paclitaxel micellar and Cremophor EL-paclitaxel [45]	Not given	Ovarian	NCT00989131	Paclitaxel (micellar)	Paclitaxel, Cremophor EL-Paclitaxel	84	Belarus, Belgium, Belarus, Croatia, Czech Republic, Denmark, Finland, Hungary, Latvia, Lithuania, Russian, Romania, Serbia, Slovakia, Sweden, Ukraine	789	Low
Chan et al. (2016)	Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer [46]	GOG 0262	Ovarian	NCT01167712	Carboplatin + paclitaxel (weekly regimen)	Carboplatin + paclitaxel (three-weekly regimen)	573	Canada, South Korea, USA	692	Some concerns
LaVigne et al. (2018)	A randomized trial of prophylactic extended carboplatin infusion to reduce hypersensitivity reactions in recurrent ovarian cancer [46]	NCT01248962	Ovarian	NCT01248962	Carboplatin (extended infusion)	Carboplatin (standard infusion)	1	USA	114	Some concerns
Kristeleit et al.	Rucaparib versus standard-of-care chemotherapy in patients with relapsed	ARIEL4	Ovarian	NCT0285594	Rucaparib	Chemotherapy (standard of	77	Brazil, Canada, Czech Republic, Hungary, Israel, Italy, Poland,	349	Some concerns

(2022)	ovarian cancer and a deleterious BRCA1 or BRCA2 mutation (ARIEL4): an international, open-label, randomised, phase 3 trial [47]					care)		Russia, Spain, Ukraine, United Kingdom, USA		
Li et al. (2016)	Olaparib With or Without Cediranib Versus Platinum-Based Chemotherapy in Recurrent Platinum-Sensitive Ovarian Cancer (NRG-GY004): A Randomized, Open-Label, Phase III Trial [48]	NRG-GY004	Ovarian	NCT02446600	Olaparib +/- cediranib	Platinum-based chemotherapy	358	Canada, Japan, South Korea, USA	565	Low
Mirza et al. (2016)	Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer [49]	ENGOT-ov16/NOVA	Ovarian	NCT01847274	Niraparib	Placebo	112	Austria, Belgium, Canada, Denmark, France, Germany, Hungary, Israel, Italy, Norway, Poland, Spain, Sweden, United Kingdom, USA	553	Low
Matei et al. (2019)	Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer [50]	GOG 0258	Endometrial	NCT00942357	Platinum chemotherapy + radiotherapy	Platinum chemotherapy only	670	Canada, South Korea, USA	736	Low
Miller et al. (2020)	Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209) [51]	GOG 0209	Endometrial	NCT00063999	Doxorubicin + cisplatin	Paclitaxel + carboplatin	650	Canada, Japan, USA	1,328	Low
Monk et al. (2016)	Randomized Phase II Evaluation of Bevacizumab Versus Bevacizumab Plus Fosbretabulin in Recurrent Ovarian, Tubal,or Peritoneal Carcinoma: An NRG Oncology/Gynecologic Oncology Group Study [52]	GOG 186-I	Ovarian	NCT01305213	Bevacizumab + fosbretabulin	Bevacizumab	51	USA	107	Low
Spirtos et al. (2019)	The addition of paclitaxel to doxorubicin and cisplatin and volume-directed radiation does not improve overall survival (OS) or long-term recurrence-free survival (RFS) in advanced endometrial cancer (EC): A randomized phase III NRG/Gynecologic Oncology Group (GOG) study [53]	GOG0184	Endometrial	NCT00006011	Doxorubicin + cisplatin	Doxorubicin + cisplatin + paclitaxel	5	USA	552	Low
Colomobo et al. (2021)	Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer [54]	KEYNOTE-826	Cervical	NCT03635567	Pembrolizumab + platinum chemotherapy	Placebo + platinum chemotherapy	151	Argentina, Australia, Canada, Colombia, France, Germany, Israel, Italy, Japan, South Korea, Peru, Russia, Spain, Taiwan, Turkey, Ukraine, USA	617	Low
Colomobo et al. (2022)	Randomized phase II trial of weekly paclitaxel vs. cediranib-olaparib (continuous or intermittent schedule) in platinum-resistant high-grade epithelial ovarian cancer [55]	BAROCCO	Ovarian	NCT03314740	Olaparib + cediranib (continuous) or Olaparib + cediranib (intermittent)	Paclitaxel	6	Italy	123	Low
Coleman et al. (2017)	Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial [56]	ARIEL3	Ovarian	NCT01968213	Rucaparib	Placebo	96	Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, United Kingdom, USA	564	Low
Coleman et al. (2017) (2)	Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre,	GOG-0213	Ovarian	NCT00565851	Arm I: Paclitaxel, docetaxel, carboplatin, bevacizumab Arm II: Gemcitabine	Paclitaxel, docetaxel, carboplatin	67	South Korea, Japan, USA	674	Low

(continued on next page)

Table 1 (*continued*)

Study	Publication title	Trial acronym	Disease indication	Trial registration number	Experimental agent(s)	Comparator agent(s)	Number of sites	Countries	Total study population (N)	Risk of bias assessment
	open-label, randomised, phase 3 trial [57]				hydrochloride, carboplatin Arm III: Gemcitabine hydrochloride, bevacizumab, carboplatin					
Penson et al. (2020)	Olaparib Versus Nonplatinum Chemotherapy in Patients With Platinum-Sensitive Relapsed Ovarian Cancer and a Germline BRCA1/2 Mutation (SOLO3): A Randomized Phase III Trial [58]	SOLO3	Ovarian	NCT02282020	Olaparib	Chemotherapy (physician's choice)	94	Argentina, Belgium, Brazil, Canada, Czech Republic, Hungary, Israel, Italy, South Korea, Mexico, Poland, Spain, USA	266	Low
Sugiyama et al. (2016)	Randomized Phase III Trial of Irinotecan Plus Cisplatin Compared With Paclitaxel Plus Carboplatin As First-Line Chemotherapy for Ovarian Clear Cell Carcinoma: JGOG3017/GCIG Trial [59]	JGOG3017/GCIG	Ovarian	000000499 (Japanese University Hospital Medical Information Network)	Irinotecan + cisplatin	Paclitaxel + carboplatin	129	Japan, South Korea, France, United Kingdom	619	Low
Tew et al. (2018)	Randomized phase II trial of bevacizumab plus everolimus versus bevacizumab alone for recurrent or persistent ovarian, fallopian tube or peritoneal carcinoma: An NRG oncology/gynecologic oncology group study [60]	GOG 186-G	Ovarian	NCT00886691	Bevacizumab + everolimus	Bevacizumab	45	USA	150	Low
Makker et al. (2022)	Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer [61]	KEYNOTE-775	Endometrial	NCT03517449	Pembrolizumab + lenvatinib	Chemotherapy (physician's choice)	169	Argentina, Australia, Brazil, Canada, Colombia, France, Germany, Ireland, Israel, Italy, Japan, South Korea, Mexico, New Zealand, Poland, Russia, Spain, Taiwan, Turkey, United Kingdom, USA	827	Low
Oza et al. (2015)	Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial [62]	Not given	Ovarian	NCT01081951	Olaparib	Paclitaxel + carboplatin	41	Australia, Belgium, Canada, Czech Republic, Germany, Italy, Japan, Netherlands, Peru, Spain, United Kingdom, USA	162	Low
Oza et al. (2015) (2)	Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase randomised trial [63]	ICON7	Ovarian	NCT00483782	Bevacizumab	Paclitaxel + carboplatin	142	Australia, France, Germany, Norway, United Kingdom	1,528	Low

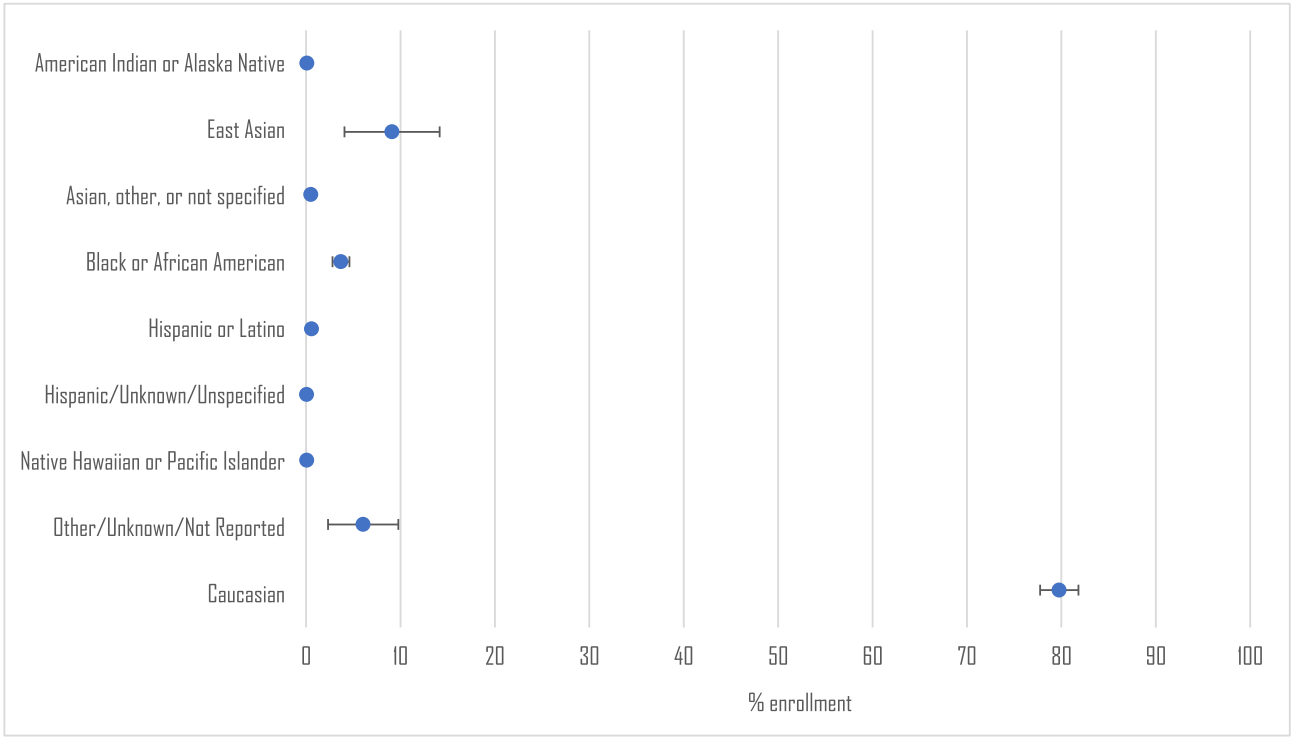

Fig. 2. Forest plot showing overall participation in RCTs by all gynecological disease indications (%). Standard error bars are shown.

Asian" ("Asian", "Asian (Chinese)", "Japanese"), "Black" ("Black/African American", "Non-Hispanic Black"), "Other" ("Other", "Unknown, Not Reported/Missing", "Non-Japanese", "Not Hispanic or Latino", "Other"), "Caucasian" ("White/Caucasian", "Non-Hispanic White"). Several publications (n=5) reported this demographic using multiple categories. For example, some studies described both "White/Caucasian" and "Non-Hispanic" categories, with both groups reported in the publication. Where multiple descriptors were reported, "ethnicity" data were extracted (e.g. "Asian", "Black/African American", "Caucasian"), as these descriptors were concordant with ethnicity terms reported in most other publications. For some studies, descriptors of ethnicity were not common with other studies ("Asian/Unknown/Other" and "Hispanic/Unknown/Unspecified" groups). In these cases, ethnicity data were extracted as reported in publications and were not grouped as above.

3.3. Location of research sites

5,478 research sites located in 44 countries were represented in included publications. 20 RCTs were conducted at sites in multiple countries, totalling n=4,867 sites. Six RCTs were conducted in one country only (5 in the US and 1 in Italy), representing 11% (n=611) of research sites. 80.1% (4390) of sites were located in North America (US, Canada and Mexico), 13.0% (714) in Europe, 3.4% (187) in East Asia (China, Japan, South Korea and Taiwan), 73 (1.3%) in the Middle East (Turkey & Israel), 72 (1.3%) in South America, 42 (0.7%) in Australasia. 78.1% (4279) of sites were located in the US alone. No sites were located in Central Asian, South Asian or African countries. Locations and numbers of research sites per country are shown in Table 3 and the distribution of sites by continent is shown in Supplementary Fig. 4.

Table 2
Total enrollment by grouped ethnicity.

Ethnicity (grouped)	Patients recruited (n)	Percentage of total (%)
American Indian or Alaska Native	18	0.1
East Asian	1552	9.1
Asian, other, or not specified	87	0.5
Black or African American	630	3.7
Hispanic or Latino	101	0.6
Hispanic/Unknown/Unspecified	12	0.1
Native Hawaiian or Pacific Islander	15	0.1
Other/Unknown/Not Reported	1031	6.1
Caucasian	13595	79.8
Total	17,041	100%

3.4. Risk of bias assessment (RoB-2)

23 of 26 studies were categorised as low risk of bias. 3 studies were categorised as "some concerns": 2 studies allowed classification of disease progression based upon clinical observation only without radiological or laboratory investigations. One study employed a non-blind trial design, investigating hypersensitivity reactions to SACT treatment as an outcome with a potentially ambiguous definition. As this review investigated participation by ethnicity and not treatment outcomes, these assessments did not exclude these articles. Risk of bias assessments are provided in Table 1, and individual domain assessments and overall risk of bias for included studies are shown as a traffic-light plot and summary schema in Supplementary Fig. 5.

4. Discussion

This review demonstrated under-representation of ethnic minority groups in gynecological cancer RCTs on the global scale, with ethnic minority groups forming low proportions of the RCT participants, and specific groups not being represented in these studies at all. This systematic review builds upon a previous review of ethnic minority enrollment in *Gynecologic Oncology Group* RCTs published 1985-2013, providing an updated and contemporaneous assessment of participation during a period where there has been a tsunami of novel therapies in gynecological cancers [11].

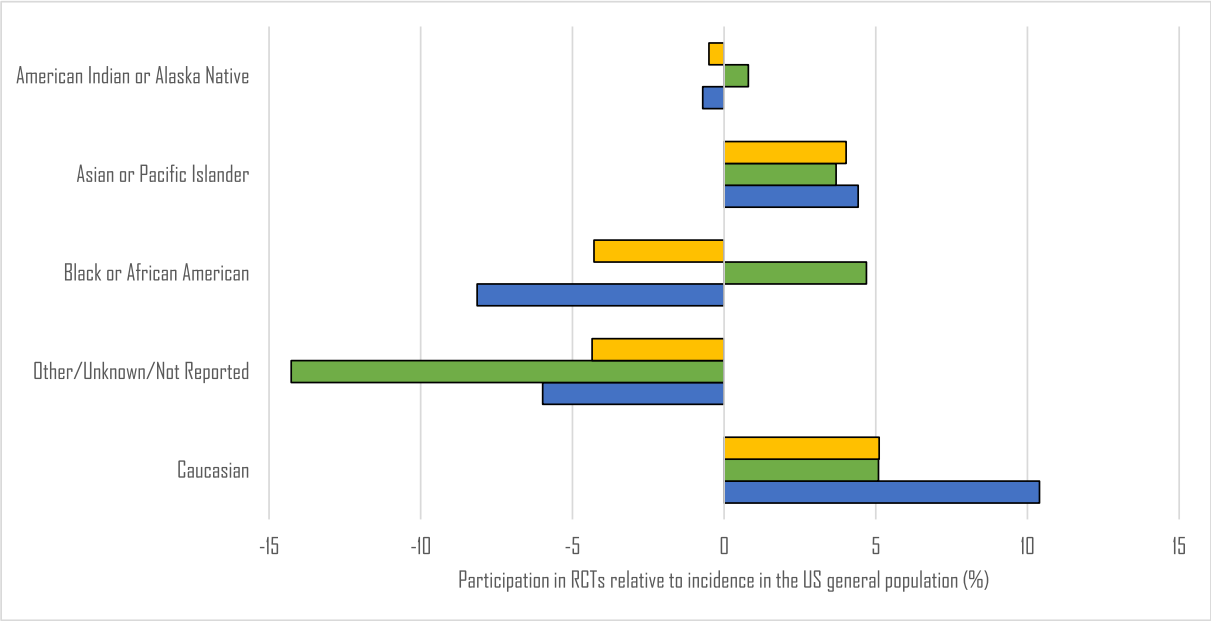

Fig. 3. Bar graph comparing the proportions of each ethnic group in RCTs to US incidence counts for endometrial, cervical and ovarian cancer populations in 2020 [21]. Positive values indicate a greater proportion of each group participating in RCTs compared to incidence in the general population, whilst negative value indicate lower participation rates in RCTs compared to incidence in the general population.

"Caucasian" patients comprised the majority of patients, forming 88% in ovarian, 68% in cervical, 73% in endometrial cancer RCTs. Representation was inadequate and extremely low for some groups, with just 8.7% and 3.7% of patients comprised of "East Asian" and "Black/African American" patients respectively. These findings are consistent with reports of Caucasian patients forming around 85% of cancer RCT populations, and 80-90% of patients in clinical trials more generally [22–24]. Low enrollment of patients from ethnic minority backgrounds is likely to limit understanding of differing treatments outcomes and toxicity profiles that may exist between groups, affecting the generalisability of findings to patients from diverse backgrounds.

The distribution of research sites showed a large skew towards North America and Europe, with 93.1% of sites located in these regions. Just 3.4% of sites were located in East Asia, 1.3% in the Middle East, 1.3% in South America and 0.7% in Australasia. Notably, no sites were located in Africa, South Asia, South-East Asia or Central Asia. For larger trials, placing research sites in multiple countries allows for faster patient recruitment and shorter timelines for drug licensing, particularly when patients with uncommon genotypes are required. The large skew in distribution of sites in Europe and North America prescribes that the majority of participants were located in these areas, which may explain some of the disparity in participation. Including more research sites in regions outside of North America and Europe may help to boost enrollment of under-served groups by increasing access to RCTs to patients from a wider range of backgrounds. Research sites are often located in urban centres, imposing further recruitment bias against patients living in rural areas [25].

Poor representation of ethnic minority groups in RCTs is likely to become a more significant issue as the incidence of gynecological cancers increases globally. In India and many Sub-Saharan African countries, ovarian and cervical cancer incidences are increasing, for example [26,27]. Whilst gynecological cancers are more common in Caucasian women, who make up 80-90% of the patient population in the US and the UK and therefore might be expected to form the majority of RCT study populations, the strong skew in research site distribution observed here is significant and likely to impact the generalisability of results [26]. Comparing 2020 US gynecological cancer incidence counts to RCT enrollment also suggests that ethnic minority patients constitute an increasingly large proportion of the patient population compared to previous reports [28]. Poor representation is therefore likely to become an increasingly significantly problem over time, as greater numbers of patients from minority backgrounds are treated with SACT for gynecological cancers globally. In cervical cancer in particular, more RCTs should be conducted in places where incidence rates are high, such as in African countries, so that treatments for patients who will receive SACT for these conditions can be tested in applicable populations.

In 1993 in the US, the National Institutes of Health (NIH) Revitalization Act was implemented, aiming to boost ethnic minority participation in clinical research by mandating inclusion of minority groups in NIH-funded research centres [29]. Several reports of the limited impact in increasing ethnic minority participation following the implementation of this policy have been reported, consistent with findings presented here [30,31]. Quotas for ethnic minority recruitment in clinical trials are not currently mandated, and may be met with opposition as 19% of clinical trials are already terminated early for failing to meet recruitment targets [32]. Opponents of this view have however dismissed this argument as an excuse for lack of effort to recruit ethnic minority patients [33].

Clinical practitioners are becoming increasingly aware of the problem of low minority representation in research and are taking efforts to address this. The NIHR-Include Ethnicity Framework established in the UK implemented in 2017 aims to boost participation of underserved groups. Language barriers, cultural beliefs around research participation and mistrust of medical institutions have been highlighted as barriers to recruitment, and many sites are assessing how to reduce the impact of these barriers [34]. High comorbidity burden has also been shown to be associated with reduced trial offering and participation in clinical trials, and is known to be a significant barrier to entry [35]. With many ethnic minority groups experiencing greater comorbidity burdens, enrollment in RCTs is likely to be impacted [36].

Clark et al. highlight key barriers to recruitment and describe communications and actions that can be taken at specific timepoints during the recruitment process, including highlighting potential benefits of RCT participation as increased monitoring of health, faster management of toxicity and closer relationships with healthcare providers [37]. Importantly, increasing awareness of RCTs was of low importance to patients.

Table 3
Number of participating sites by country and global region.

Region	Countries	Number of sites	Total number of sites	% of total
North America	USA	4,279	4,390	80.1%
	Canada	96		
	Mexico	15		
South America	Argentina	19	72	1.3%
	Brazil	26		
	Chile	5		
	Columbia	13		
	Peru	9		
Europe	Austria	10	714	13.0%
	Belarus	4		
	Belgium	23		
	Bulgaria	3		
	Croatia	3		
	Czech Republic	23		
	Denmark	6		
	Estonia	1		
	Finland	5		
	France	74		
	Germany	112		
	Greece	5		
	Hungary	14		
	Ireland	1		
	Italy	70		
	Latvia	1		
	Lithuania	2		
	Netherlands	5		
	Norway	5		
	Poland	35		
	Romania	7		
	Russia	66		
	Serbia	4		
	Slovakia	3		
	Spain	79		
	Sweden	10		
	Ukraine	32		
	United Kingdom	111		
Asia	China	14	187	3.4%
	Japan	107		
	South Korea	51		
	Taiwan	15		
Australasia	Australia	41	42	0.8%
	New Zealand	1		
Middle East	Israel	54	73	1.3%
	Turkey	19		
Total			5,478	100%

Willingness to participate in RCTs reportedly does not differ significantly between patients of different ethnicity, suggesting that strategies to boost participation can be effective if implemented appropriately [34]. Improving communication around trial participation, developing literature in patient's own languages and including research staff from ethnic minority backgrounds to improve institutional trust have been proposed as possible strategies to boost minority enrollment in research [38]. Increased monitoring of recruitment at the individual site level is also now underway at many sites in the UK, however, the impact of National Institute for Health and Care Research policy NIHR-Include and other targeted recruitment strategies will not be clear for some time [39].

Under-representation of ethnic minority groups is a widespread issue in many disciplines of clinical research, including cardiovascular disease, mental health, and more recently COVID-19 research [40,41]. In oncology, evidence of pharmacogenomic evidence of disparate treatment effects between patients of different ethnicity due to genetic variation is likely to become more clearly understood over time [42]. As the numbers of gynecological cancer patients increases globally, particularly in developing countries, new challenges may emerge in maximising treatment benefit whilst reducing toxicity burden in diverse ethnic groups treated with SACT. The studies presented here show a marked lack of sites in South Asia, South-East Asia and Africa. The low proportion of "East Asian" patients participating, for example, may lead to disparate treatment effects arising in this minority group, as demonstrated previously in the JGOG3016 and ICON8 studies in ovarian cancer [8,9]. Subgroup analyses of specific ethnic groups using real-world data have been performed by some authors to evaluate the suitability of SACT in specific cohorts where representation in RCTs was low; however, these studies are time-consuming and can be avoided by improving participation of ethnic minorities in RCTs [43]. In this review, data were not collected on the number of RCTs conducting subgroup analyses, although other authors have reported 25-32% of studies analysing results by ethnic group in cancer clinical trials [44,45]. Conducting subgroup analyses at the RCT stage of drug development may reveal disparate treatment effects earlier, reducing the need for future observational research.

4.1. Race and ethnicity reporting

There is currently no guidance on the usage of race and ethnicity reporting terms in RCTs [46]. Recruitment by ethnicity is not currently included in quality assessment frameworks for RCTs, and is not considered a measure of study quality [47]. Ethnicity terminology can also differ between regions. For example, "Asian" ethnicity in the US is likely to refer to "East Asian", whilst in Europe it would likely refer to a "South Asian" patient. Additionally, some groups reported in recruitment figures are relevant only to specific countries; patients of "Hispanic or Latino" ethnicity, for example, do not form significant populations in Europe or Asia, and would be categorised as "Other" ethnicity.

Significant levels of discordance between self-reported race or ethnicity and those recorded by healthcare practitioners in electronic health record systems have been reported [48]. Furthermore, ethnicity terms in the US are defined by census guidelines implemented in 1997, which describe broad ethnicity categories that do not necessarily represent every person's perceived identity [4]. Proposals have also been made to amend race and ethnicity definitions to use more specific terms in the US in 2024, which could improve reporting of these demographics in RCTs [49]. Ideally, terms would be standardised globally; however this is unlikely to be possible due to cultural and historical differences surrounding the use of race and ethnicity terminology [50]. Additionally, the gathering of racial or ethnicity data is an illegal practice in France and is not commonly practiced in Germany, where a significant number of research sites were placed in this review. This practice will further limit the quality of ethnicity reporting in RCTs. Grouping by broad race/ethnicity terms limits comparisons of participation between regions; however, the aim of this review was to produce an overall summary of ethnic minority representation in clinical trials, which was possible using the data available.

4.2. Strengths and limitations

In this review, the 26 RCTs met inclusion criteria over a 10-year period, providing a large representative sample of patients recruited to contemporary gynecological cancer RCTs. The low rate of reporting of ethnicity, as well as the frequent use of "Unspecified" or "Unknown" ethnicity terms limited the assessment of representation and may represent some reporting bias. Many trials also reported broad ethnicity categories, rather than more specific descriptions. The issue of missing reporting of ethnicity has been raised previously, with authors highlighting the need for patients to report their own ethnicity instead of having these data entered by clinicians [51]. Baseline characteristics of RCT cohorts are reported as aggregated totals, which does not allow for a granular assessment representation of enrollment for individual sites or countries. Additionally, when comparing the representation of ethnic minority groups in RCTs to real-world populations, comparisons can only be made to countries where incidence data by ethnicity are available. Here, comparisons could be made to US and UK incidence counts for 2020 as these data were available. Comparing the RCT

population to demographics in countries outside of North America and Europe would give a very different picture of representation, with significant under-representation of the majority population. However, comparisons to populations in other regions could not be made as these data were not available. Comparison to the US population was considered most appropriate given that the majority of research sites were located in the US. Despite these limitations, this systematic review has provided a contemporary description of participants that have taken part in RCTs for novel therapies that are now routinely used in clinical practice in gynecological cancers, highlighting the widespread issue of disparity in participation and providing a reference population for future important work investigating treatment disparity between subgroups of gynecological cancer patients.

5. Conclusions

This review showed poor representation of ethnic minority groups on the global scale, with a majority "Caucasian" RCT population. More work is needed at local and country levels to understand how research sites are representing their patients. Improving participation of underserved groups is likely to improve generalisability of results from RCTs and broaden understanding of treatment outcomes for patients from diverse ethnic backgrounds. This work informs RCT recruiting practices and future observational research into treatment outcomes for gynecological cancer patients by providing a contemporary assessment of the population that enrolled in RCTs leading to licensing for novel therapies now routinely used in gynecological cancers.

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CRediT authorship contribution statement

Luke Steventon: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Shibani Nicum:** Supervision, Writing – review & editing. **Kenneth Man:** Conceptualization, Supervision, Writing – review & editing. **Ubonphan Chaichana:** Data curation, Validation. **Li Wei:** Supervision, Writing – review & editing. **Pinkie Chambers:** Supervision, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.01.052.

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