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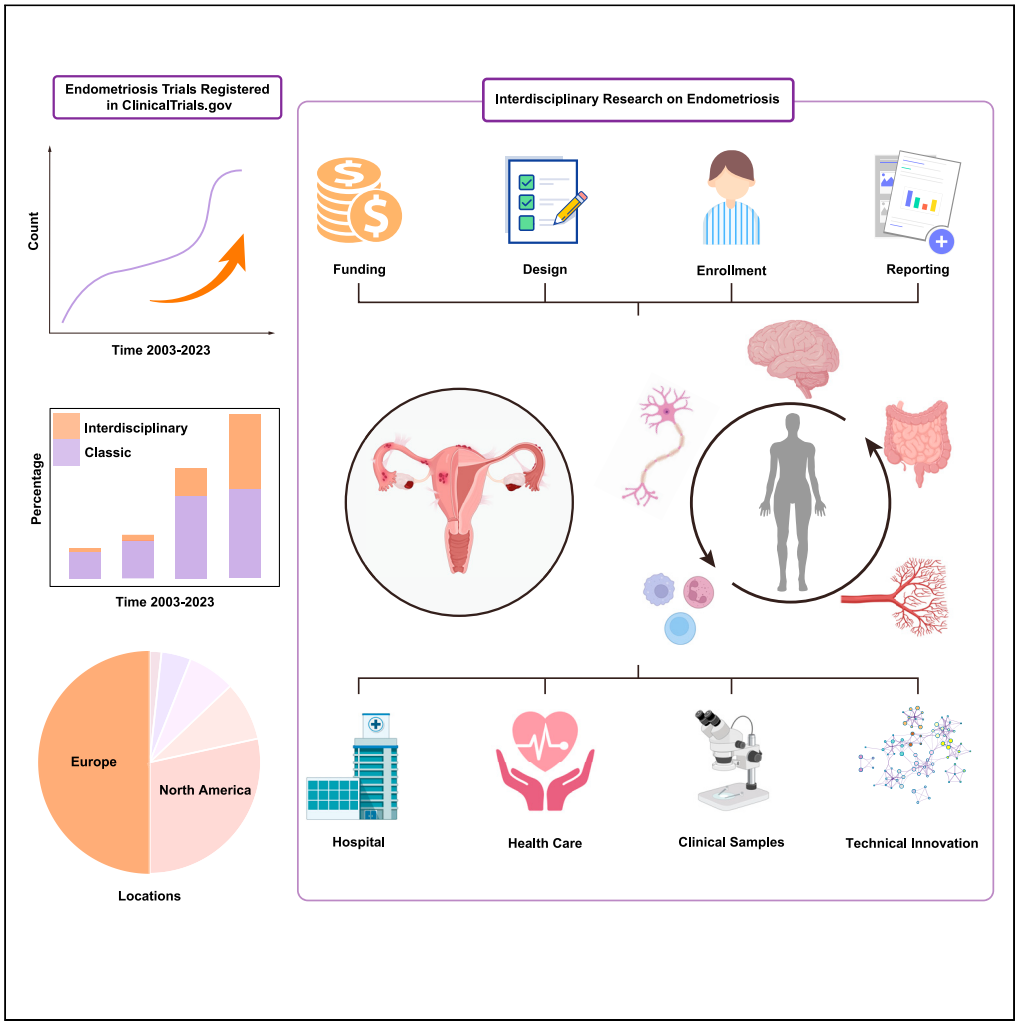

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Highlights

Interdisciplinary trials on endometriosis are experiencing rapid growth

Patient-centered multidisciplinary management represents the future direction

Employing interdisciplinary approaches comes with challenges in research

Deeper understanding of endometriosis requires more interdisciplinary collaboration

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An overview and comprehensive analysis of interdisciplinary clinical research in endometriosis based on trial registry

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SUMMARY

Endometriosis is a chronic multisystem disease associated with immunological, genetic, hormonal, psychological, and neuroscientific factors, leading to a significant socioeconomic impact worldwide. Though multidisciplinary management is the ideal approach, there remains a scarcity of published interdisciplinary clinical trials at present. Here, we have conducted a comprehensive analysis of the characteristics and issues of interdisciplinary trials on endometriosis based on the clinical registration database ClinicalTrials.gov. Among all 387 endometriosis trials, 30% (116) were identified as interdisciplinary, mostly conducted in Europe and North America, and fully funded by non-industrial sources. We documented growth in both patient-centered multidisciplinary comprehensive management and collaboration between fundamental biomedical science and applied medicine. However, compared to traditional obstetric-gynecological trials, interdisciplinary studies exhibited negative characteristics such as less likely to be randomized and less likely to report results. Our study provides insights for future trial investigators and may contribute to fostering greater collaboration in medical research.

INTRODUCTION

Endometriosis is a common chronic gynecological condition characterized by ectopic presence of endometrial-like tissue outside the uterine cavity, with typical pelvic manifestations such as dysmenorrhea, chronic pelvic pain, and infertility.[1] The condition affects about 10% of the global female population, involving approximately 190 million patients,[2] and a significant portion is unable to access timely, accurate diagnosis as well as effective treatment.[3] Endometriosis affects professional functioning, quality of life, mental wellbeing,[4] and imposes a substantial economic burden.[5] It is also associated with obstetric complications such as gestational diabetes,[6] placental dysfunction,[7] and hypertensive disorders of pregnancy, bringing potential risks of multiple adverse maternal, fetal, and neonatal outcomes.[8–10] Moreover, a growing number of recent studies advocate for recognizing and managing endometriosis as a multisystem disease rather than just an obstetrics and gynecology condition.[2,11] Symptomatically, it encompasses various clinical manifestations beyond the female reproductive system, including migraine,[12] depression, and eating disorders.[4] Patients with endometriosis are also more likely to experience a range of pelvic and extrapelvic comorbidities, such as cancer,[13] autoimmune diseases,[14] allergic disorders,[15] and cardiovascular issues.[16] Therefore, relying solely on interventions provided by obstetrician-gynecologists, mainly including pharmacological treatment, surgery, and assisted reproductive technology (ART), offers limited efficacy. A patient-centered multidisciplinary long-term strategy could be the ideal management paradigm.[17]

The peer-reviewed literature constitutes the primary and foundational source of information for the development of clinical guidelines and reviews. Despite the increasing discussion on non-pharmacological strategies, such as nutrition,[18] exercise,[19] and other approaches for alleviating symptoms of endometriosis, as well as the continual emergence of new potential targets and therapeutics in the fields of molecular biology and bioengineering,[20–22] there is still a lack of clinical evidence regarding the specific effectiveness and risks of any interdisciplinary intervention.[23] Animal models provide extensive opportunities for biological experiments and translational research, but inherent limitations exist due to the disparities with human physiology.[24,25] Clinical evidence guides clinical practice, and well-designed randomized controlled trials (RCTs) play an irreplaceable role in advancing medical interventions and management approaches.

Endometriosis necessitates a multidisciplinary approach in both management and research. However, there is still a paucity of published interdisciplinary trials on endometriosis, and the existing data are insufficient to portray their overall developmental status. Clinical trials are

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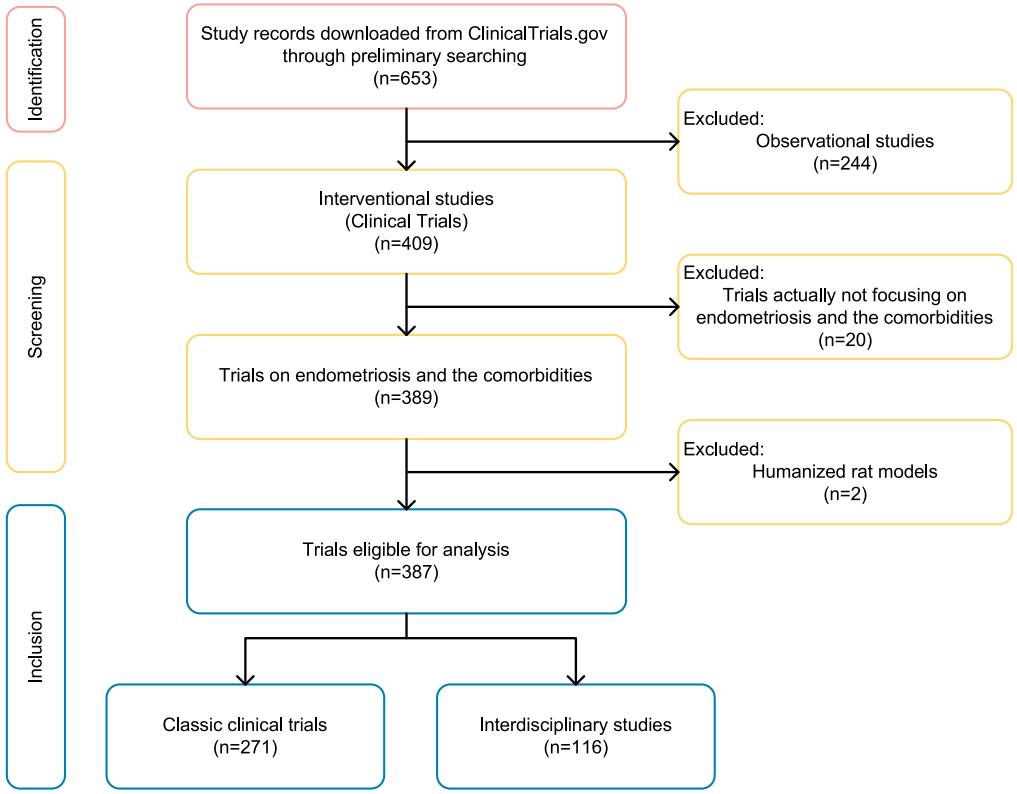

Figure 1. Flow chart showing the screening process

mandated to be registered in publicly accessible registries,[26] as a mechanism to foster standardized management and control the dissemination biases resulting from selective reporting. ClinicalTrials.gov is the world's largest clinical trial registration database, encompassing a result reporting database as well.[27] It provides valuable resources for accessing the characteristics and progress of clinical trials in specific medical fields.[28,29] Our study aimed to comprehensively analyze all clinical trials related to endometriosis registered in the ClinicalTrials.gov database. From the perspective of obstetrician-gynecologists, we aimed to identify the interdisciplinary studies and investigate the overall landscape and characteristics, such as quantity, status, enrollment size, locations, funding sources, outcome measures, research topics, and other design details. We also aimed to explore whether interdisciplinary trials were more prone to early termination or lack of result reporting and to discuss the development and challenges of interdisciplinary trials in endometriosis research.

RESULTS

Of all 4,57,254 records from 221 countries registered in the ClinicalTrials.gov database as of June 30, 2023, 653 studies were identified according to the searching strategy. After screening, 387 clinical trials on endometriosis were finally included for analysis (Figure 1). Taking into account intervention types, investigator departments, and research topics, 116 studies were categorized as interdisciplinary trials, while the remaining 271 were classified as classic clinical trials.

Temporal and spatial information

The commencement dates of the trials encompassed a time span of more than 20 years, ranging from the earliest trial initiated on November 1, 1998, to the latest trial expected to start in 2024. Over the past two decades, the number of registered clinical trials on endometriosis increased gradually and continuously (Figures 2A and 2B). Among these trials, the number of interdisciplinary studies showed an apparent increase after 2018 and reached the peak in 2022 (n = 25). During the five-year period from 2018 to 2022, interdisciplinary trials accounted for 41.5% (73/176) of the total.

The trials were conducted in more than fifty countries or regions across the whole of the six continents (except Antarctica) (Figure 2C). Nearly half of the trials were conducted in Europe (169/387, 43.7%), followed by North America (120/387, 31.0%), Asia (71/387, 18.3%), Africa (26/387, 6.7%), Middle East (22/387, 5.7%), South America (16/387, 4.1%), and Oceania (8, 2.1%). Similarly, interdisciplinary trials were also predominantly conducted in Europe (58/116, 50%) and North America (33/116, 28.4%) (Figure 2D). All the 16 intercontinental studies were classic trials focused on drug research and development (Drug R&D), entirely funded by industry.

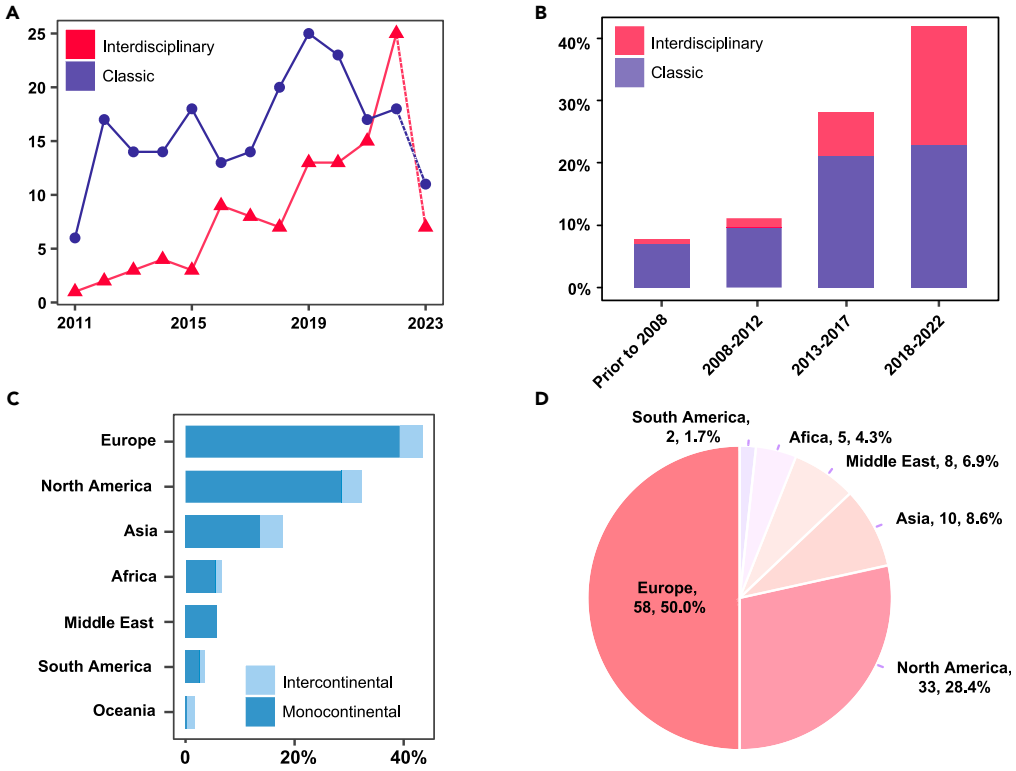

Figure 2. Commencement dates and geographic locations of clinical trials on endometriosis registered in ClinicalTrials.gov

(A) The number of interdisciplinary and classic trials initiated annually since 2011, as of June 30, 2023.

(B) Trials initiated within 5-year periods.

(C) The geographic locations of all clinical trials.

(D) The geographic locations of interdisciplinary trials.

Registration, status, and phases

Over half of the trials on endometriosis were registered after initiation (215/387, 55.6%), and the retrospective registration rates were similar between classic and interdisciplinary studies (56.5% vs. 53.4%, p = 0.585) (Table 1). Most interdisciplinary trials were still recruiting (40/116, 34.5%) or not yet started recruitment (16/116, 13.8%) at the time of analysis, and only a quarter had been completed (29/116, 25%). Similar proportion of the two subgroups was in unknown status (16.4% vs. 14.4%), which means the investigators had not updated the records for at least 2 years and the expected completion time had passed. Most interdisciplinary trials (86/116, 74.1%) were not applicable for clinical phases as defined by the Food and Drug Administration (FDA), and nearly one-tenth (11/116, 9.5%) were in clinical phase 2. Nearly half of the classic trials (127/271, 46.9%) were in clinical phase 2 to 3.

Sponsor, funding source, and results reporting

The vast majority of interdisciplinary trials were sponsored by non-industry entities, mainly including universities, academic institutions, and medical centers. Only 14 interdisciplinary trials received funding from industry, and fewer reported National Institutes of Health (NIH) funding. However, considering that the NIH serves as the largest biomedical funding agency to support research projects in universities and research institutions across the United States, the actual number of trials received supports from the NIH could be more. In fact, most of the clinical trials on endometriosis (including both classic and interdisciplinary studies) were sponsored and promoted by the academic community, especially in recent 5 years.

Interdisciplinary trials were less likely to provide any partial or complete study results in the database (p = 0.001). Taking into account the various trial status, the difference still held statistical significance after excluding all trials that began recruitment for less than 6 months at the time of analysis.

Design characteristics

Among all endometriosis clinical trials, the utilization of randomized design (280/383, 73.1%) and blinding (196/383, 51.2%) was relatively common. However, compared to the classic trials, interdisciplinary trials were less likely to be randomized (53.4% vs. 81.6%, p < 0.001) and more

Table 1. General characteristics of interdisciplinary and classic clinical trials on endometriosis registered in the ClinicalTrials.gov database

		Research category		
Clinical trial characteristics	Total (n = 387)	Interdisciplinary studies (n = 116)	Classic clinical trials (n = 271)	p value
Registered retrospectively[a]	215(55.6)	62(53.4)	153(56.5)	0.585
Status				
Completed	159(41.1)	29(25.0)	130(48.0)	<0.001
Recruiting[b]	90(23.3)	40(34.5)	50(18.5)	
Active, not recruiting	17(4.5)	6(5.2)	11(4.1)	
Not yet recruiting	31(8.0)	16(13.8)	15(5.5)	
Not in process[c]	32(8.3)	6(5.2)	26(9.6)	
Unknown status	58(15.0)	19(16.4)	39(14.4)	
Phases				
Early Phase 1	8(2.1)	6(5.2)	2(0.7)	<0.001
Phase 1	23(5.9)	3(2.6)	20(7.4)	
Phase 1|Phase 2	9(2.3)	3(2.6)	6(2.2)	
Phase 2	84(21.7)	11(9.5)	73(26.9)	
Phase 2|Phase 3	10(2.6)	1(0.9)	9(3.3)	
Phase 3	47(12.1)	2(1.7)	45(16.6)	
Phase 4	37(9.6)	4(3.4)	33(12.2)	
Not Applicable	169(43.7)	86(74.1)	83(30.6)	
Sponsor type				
Industry	113(29.2)	8(6.9)	105(38.7)	<0.001
Non-industry	274(70.8)	108(93.1)	166(61.3)	
Funding source[d]				
Industry	125(32.3)	14(12.1)	111(41.0)	NA
NIH	13(3.4)	5(4.3)	8(3.0)	
Other	276(71.3)	107(92.2)	169(62.4)	
Multicenter	112(30.4)	16(13.8)	96(35.4)	<0.001
Results available	37(9.6)	2(1.7)	35(12.9)	0.001
Enrollment size	67(34–122)	52(30–100)	79(38–159)	0.005
Follow-up duration (m)	21(11–33)	19(11–31)	22(12–34)	0.171
Allocation	n = 383	n = 116	n = 267	
Randomized	280(73.1)	62(53.4)	218(81.6)	<0.001
Non-Randomized	38(9.9)	20(17.2)	18(6.7)	
Not Applicable	65(17.0)	34(29.3)	31(11.6)	
Intervention model	n = 385	n = 116	n = 269	
Parallel	286(74.3)	74(63.8)	212(78.8)	0.011
Single Group	79(20.5)	35(30.2)	44(16.4)	
Crossover	12(3.1)	5(4.3)	7(2.6)	
Sequential	6(1.6)	1(0.9)	5(1.6)	
Factorial	2(0.5)	1(0.9)	1(0.9)	
No. of arms	n = 384	n = 115	n = 269	
1	74(19.3)	34(29.6)	40(14.9)	<0.001
2	230(59.9)	68(59.1)	162(60.2)	
≥3	80(20.8)	13(11.3)	67(24.9)	
Masking	n = 383	n = 115	n = 268	
None (open label)	187(48.8)	69(60.0)	118(44.0)	0.004
Blind	196(51.2)	46(40.0)	150(56.0)	

Abbreviations: NIH, National Institutes of Health; m, months; NA, not applicable.
[a]Registration after the trial start date.
[b]Including status of enrolling by invitation.
[c]status of suspended, terminated and withdrawn.
[d]A single trial could have multiple sources of funding therefore the comparison was not conducted. Twenty trials received funding from both industry and other entities, and 7 studies received funding from both NIH and other entities.

likely to be open-label (60% vs. 44%) and conducted at a single site (86.2% vs. 64.6%). In addition, the enrollment size of interdisciplinary trials was smaller than that of classic trials (52 [IQR 30–100] vs. 79 [IQR 38–159], p = 0.005), but the difference in follow-up duration between the two was not statistically significant (19 [IQR 11–31] vs. 22 [IQR 12–34], p = 0.171). Parallel assignment was the most common intervention model. Interdisciplinary trials were more likely to have a single group design (30.2% vs. 16.4%), while classic trials were more likely to have three or more study arms (24.9% vs. 11.3%).

Population and outcome measures

Regarding the target population (Table 2), approximately one-fifth of the trials recruited healthy volunteers. Five of the classic trials specifically enrolled postmenopausal healthy volunteers and were conducted by pharmaceutical companies for pharmacokinetic and/or pharmacodynamic studies. In addition to serving as healthy controls, interdisciplinary trials also recruited patients' family members or partners as part of the behavioral or comprehensive intervention. Slightly more interdisciplinary trials recruited adolescent participants, but overall, the registered clinical trials for endometriosis were predominantly focused on women of reproductive age. Continuing the in-depth analysis of the details of inclusion and exclusion criteria, interdisciplinary collaborators preferred to design studies without restricting the types of endometriotic lesions (98/116, 84.5%), disease staging, or classification (114/116, 98.3%). In contrast, a relatively greater proportion of classic trials were focused on ovarian endometriomas (16.2% vs. 6.9%).

The majority of both classical trials (82/116, 71.3%) and interdisciplinary trials (194/271, 72.4%) reported only one primary outcome measure (Table 2). Classical trials were more likely than interdisciplinary trials to report at least one secondary endpoint, but the proportion of studies setting three or more secondary (and additional) outcome measures was similar (54.8% vs. 53.0%). Pain was the most frequently used outcome classification (Figure 3, See also Table S1), including a variety of individual or composite indicators. In addition to evaluating gynecological symptoms such as dysmenorrhea, chronic pelvic pain, and deep dyspareunia, both classic and interdisciplinary trials involved endpoints concerning extra-pelvic pain, such as headaches, back pain, or just described as general pain relief. Compared with classic studies, interdisciplinary trials were more likely to report quality of life and biological parameters as the primary outcomes, and the difference persisted when considering all outcome measures. They were also less likely to report safety (adverse events) as the primary endpoints, but the difference was minimal when considering all endpoints. It is noteworthy that the proportion of trials with fertility outcomes was relatively modest (49/387, 12.7%), and interdisciplinary studies were less likely to work on infertility (n = 4 in primary outcomes; n = 8 in all outcomes).

Research topics and evolving patterns

In order to systematically categorize the research topics of ongoing studies, and gain insights into the latest unpublished findings, we extracted trials started since 2018 (n = 194) from all included studies and categorized them based on sponsors and interventions (Figure 4). The industry's focus primarily lied in drug R&D, while trials from non-industry sources presented greater diversity in terms of both interventions and research topics. The interdisciplinary trials (82/194, 42.3%) encompassed all aspects of endometriosis, including basic scientific research, diagnostic testing, therapeutic management as well as supportive care. From the perspective of intervention type, trials working on adjuvant therapies (n = 44, 40 from non-industry) and exploratory testing (for basic science research, n = 19) were all associated with interdisciplinary collaborations, and a smaller subset of interdisciplinary studies involved diagnosis (n = 9), multidisciplinary surgeries (n = 4), specialized analgesic prescriptions (n = 5), and biologicals (categorized in drugs, n = 1).

Most of the interdisciplinary trials were still ongoing at the time of analysis (65/82, 79.3%), 7 were completed, 9 in unknown status, and 1 was withdrawn due to misregistration under the wrong sponsor. None of these 82 interdisciplinary trials provided any partial or complete results in the registration database. By searching the NCT identifiers in the open medical literature databases (such as PubMed), we only identified one published trial (NCT04650516) among interdisciplinary trials started since 2018, which reported the role of a virtual reality immersive therapy in alleviating pelvic pain among woman suffering from endometriosis.[30] Besides that, the most recent interdisciplinary RCT (NCT03125304) started in May 2017 and published in May 2023, reported the efficacy of acupuncture in addressing endometriosis-associated pain, although the effects diminish after treatment discontinuation.[31] In contrast, twelve publications were identified from classic trials started after 2018, mainly involving gonadotropin-releasing hormone receptor antagonists,[32,33] pre-*in vitro* fertilization (IVF) medication,[34] surgery, and ovarian function preservation.[35]

Slightly over half of the interdisciplinary trials were randomized (44/82, 53.7%), but mostly small-sample-sized single-center studies. Only 13 (13/82, 15.9%) studies were RCTs recruiting for 100 or more participants (Table 3), involving digital therapeutics, multidisciplinary surgery, and collaborations with psychotherapists, physiotherapists, nutritionists, primary care practitioners as well as biochemistry scientists. Among these, 9 trials were ongoing, 2 trials were completed, and 2 were in unknown status.

Table 2. Population and outcome characteristics

Population and Outcomes	Total (n = 387)	Research Category		p value
		Interdisciplinary studies (n = 116)	Classic clinical trials (n = 271)	
Healthy volunteers	73(18.9)	22(19.0)	51(18.8)	0.973
Adolescent participants[a]	15(3.9)	8(6.9)	7(2.6)	0.044
Condition				
Endometriosis[b]	295(76.2)	98(84.5)	197(72.7)	0.035
Ovarian endometrioma	52(13.4)	8(6.9)	44(16.2)	
Deep endometriosis	31(8.0)	9(7.8)	22(8.1)	
Others	9(2.3)	1(0.9)	8(3.0)	
Staging/Classification				
Undefined	363(93.8)	114(98.3)	249(91.9)	0.017
Reported	24(6.2)	2(1.7)	22(8.1)	
No. of primary outcomes	n = 383	n = 115	n = 268	
1	276(72.1)	82(71.3)	194(72.4)	0.599
2	54(14.1)	19(16.5)	35(13.1)	
≥3	53(13.8)	14(12.2)	39(14.6)	
No. of other outcomes	n = 383	n = 115	n = 268	
0	74(19.3)	31(27.0)	43(16.0)	0.009
1	60(15.7)	9(7.8)	51(19.0)	
2	44(11.5)	12(10.4)	32(11.9)	
≥3	205(53.5)	63(54.8)	142(53.0)	

[a]Participants under the age of eighteen.
[b]Trials with the inclusion of multiple subtypes or without restrictions on endometriosis lesions.

DISCUSSION

Main findings

Our study conducted a comprehensive analysis of registered interdisciplinary trials for endometriosis based on the ClinicalTrials.gov database. A total of 387 trials on endometriosis were included in the analysis, and approximately 30% of them involved interdisciplinary collaboration, with two-thirds still ongoing as of June 30, 2023. There has been a noteworthy growth in the registration of interdisciplinary trials, the majority of which are actively advancing. Our analysis provides evidence of growth in patient-centered multidisciplinary management and collaboration between fundamental biomedical science and applied medicine.

However, development coexists with challenges. In comparison to traditional obstetric-gynecological trials, interdisciplinary studies were generally of smaller scale, with negative design characteristics (for example, less likely to be randomized or blinded), and less inclined to provide any result in the database. Most importantly, only a minimal fraction of the completed interdisciplinary trials reached publication. On the other hand, we did not observe a higher tendency for interdisciplinary studies to experience early termination or lack of funding based on the current data. In fact, some early classic trials reported premature terminations due to insufficient funding.

Interpretations and insights

Endometriosis is a chronic disease associated with debilitating pain and infertility,[1] affecting about 5–10% of women of reproductive age worldwide, it brings significant health concerns as well as economic burdens.[3] With an evolving understanding of the etiology and pathophysiology, endometriosis is increasingly recognized as a systemic disease[11] and the traditional model centered around obstetrician-gynecologists is insufficient to meet the extensive clinical needs. Interdisciplinary collaboration promotes timely diagnosis, effective treatment, and advances fundamental scientific research. In this context, our study provided additional evidence of the growth in interdisciplinary trials on endometriosis research, along with accompanying challenges. Qualitatively, these studies exhibit heterogeneity in primary purposes and present a rational and disease-associated distribution. The anatomical severity of endometriosis lesions does not necessarily reflect the severity of patient symptoms. Therefore, treatment strategies typically focus on alleviating symptoms rather than addressing the disease itself.[2,36] Correspondingly, we found that most interdisciplinary trials focused on the comprehensive management of symptoms. In the remaining studies, a subset was dedicated to diagnostic endeavors, while another subset collaborated with scientists from diverse domains to investigate the disease itself and unravel its underlying biological mechanisms.

We found an increasing number of trials working on interdisciplinary management, with quality of life and patients' overall subjective experiences as (part of) the outcome measures. This reflects the evolving paradigm of patient-centered comprehensive management. Pain and

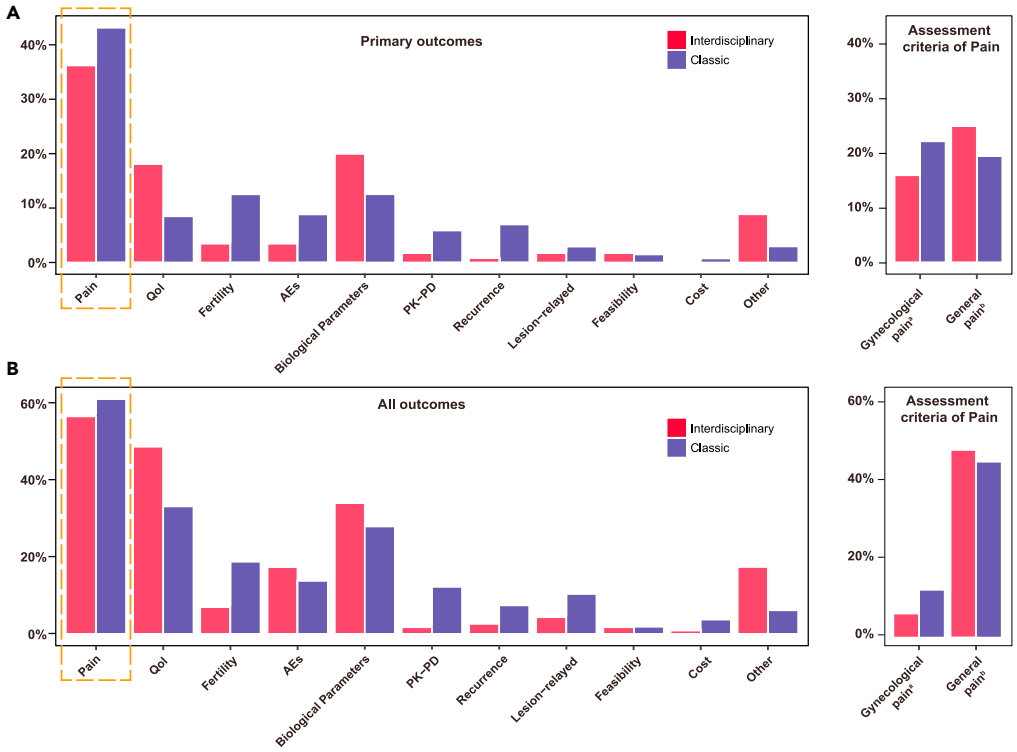

Figure 3. Comparison of the proportions of outcome measures between interdisciplinary (n = 115) and classic (n = 268) trials on endometriosis

Abbreviations: QoL, quality of life; AEs, adverse events; PK-PD, pharmacokinetics-pharmacodynamics.

[a] Including chronic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, and dysuria, with most studies concentrating on chronic pelvic pain associated with endometriosis.

[b] Including all potential pelvic or extrapelvic pain symptoms associated with endometriosis.

(A) Primary outcomes.

(B) All outcomes, including primary, secondary, and other additional outcomes.

infertility are the most typical symptoms of endometriosis, as 45–80% of women with pelvic pain and 20–50% of women experiencing infertility may be afflicted by endometriosis.[37–39] In our sample, most interdisciplinary trials were related to endometriosis-associated pain, involving collaboration among gynecologists, other specialists, general practitioners, rehabilitation therapists, and healthcare providers. The interventions included nutrition, exercise, electrotherapy, psychological support, and digital therapeutics. Additional trials on alternative therapies related to geographic characteristics, such as acupuncture[31,40] and herbal remedies,[41] were supplementary identified from other registries, including those in Asia and Australia. The prospect of accumulating clinical evidence for comprehensive management of endometriosis-associated pain in the near future is optimistic. However, this does not imply a lack of funding and trials in infertility research. In fact, trials related to infertility were nearly doubled the number of those related to endometriosis in ClinicalTrials.gov. But most of these studies focused on pregnancy-related outcomes and only about 1% of them mentioned endometriosis.[29] Based on the clinical evidence, there is currently no clear consensus on the optimal approach for endometriosis-associated infertility, particularly for the management of endometriomas before assisted reproduction.[2,23] Accordingly, more well-designed population-specific trials are needed in the future to address the crucial question: which interventions can maximally enhance and/or maintain fertility in women diagnosed or suspected with endometriosis? This includes trials on both classical obstetric-gynecological interventions and interdisciplinary approaches.

In trials on endometriosis diagnosis, we observed an increasing collaboration between gynecologists and imaging experts. The advancement of imaging techniques involves not only more accurate non-invasive diagnostics but also real-time intraoperative imaging technologies, aimed at facilitating intraoperative diagnostics, reducing operation time, and mitigating postoperative complications. In the realm of biomarkers, it may be attributed to the fact that many candidate biomarkers investigated in earlier studies have proven unsuitable for large-scale clinical translation.[11,42] Among trials started after 2018, only one industry-sponsored study (NCT03376451) was identified to conduct large-scale biomarker screening. Other potentially relevant trials were categorized as exploratory studies due to their involvement in investigating more in-depth molecular mechanisms, with the aim of advancing our understanding of the disease.

We noted a growing interest among scientists of diverse backgrounds in endometriosis research, as evidenced by the increasing number of ongoing exploratory trials covering the immunological microenvironment, metabolomics, microRNAs, neuroscience, epidemiology, and other fields. These studies not only focused on the mechanisms of endometriosis-associated pain and infertility but also investigated the systemic effects of endometriosis, such as the related role of estrogen in endothelial dysfunction and cardiovascular disease risk

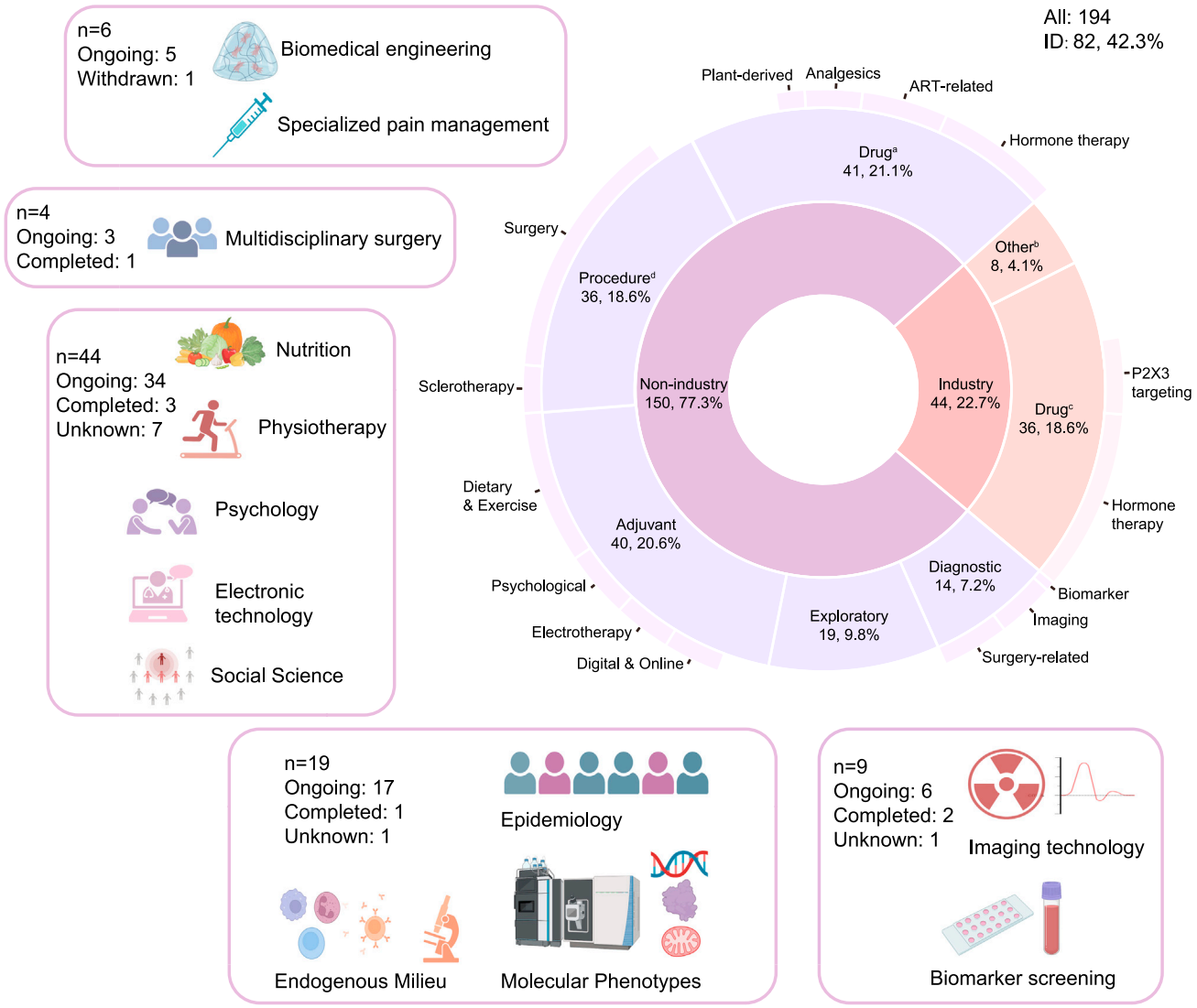

Figure 4. All trials started since 2018 (n = 194) were categorized by sponsor type, intervention, and research topic

Surrounding details encompass the content, quantity, and status of interdisciplinary trials (n = 82) at the time of analysis. Some materials were sourced from BioRender.com.

Abbreviations: ID, interdisciplinary; ART, assisted reproductive technology, P2X3, P2X ligand-gated ion channel 3.

[a] Including compounds and biological agents. Drug trials related to ART were not repetitively accounted in hormone therapy. Other drugs included dichloroacetate, cabergoline, selective oxytocin receptor inhibitor, oral probiotics and/or antibiotics, metronidazole, aspirin, melatonin, granulocyte colony-stimulating factor, and autologous NK cell therapy.

[b] Including high intensity focused ultrasound (HIFU), 1 diagnostic test and 4 no-medical interventions.

[c] Other drugs included quinagolide vaginal ring, vaginal suppositories, HMI-115, MT-2990, BAY2395840, and BAY2328065.

[d] Others included percutaneous radiofrequency ablation (PRFA), cryoablation, endometrial scratching, and *trans*-vaginal aspiration.

(NCT03746535). In recent years, there have been a number of well-designed interdisciplinary observational studies reporting the molecular mechanisms[43–45] and systemic impacts[46,47] associated with the onset and progression of endometriosis. The potential models and mediators include the genetic/epigenetic theory,[47–49] the neuroendocrine peptide kisspeptin system,[50] blood metabolites,[51] circulatory proteins,[52,53] systemic inflammatory mediators and molecules.[36] While the number of relevant clinical interventional studies is currently limited, cutting-edge trials are continuously emerging, actively progressing, and additional findings may subsequently be translated into clinical applications in the future. However, it is also important to acknowledge that we are still in the very early exploratory stage. Despite the systemic approach taken in addressing endometriosis, there is still a notable scarcity of studies employing a multi-omics approach to investigate the disease.[54] It will continue to necessitate further interdisciplinary collaboration and technological innovation to address this gap in current research.

Table 3. Interdisciplinary RCTs on endometriosis with at least 100 participants since 2018

NCT Number	Intervention/Topic	Funding	Location	Status	Enrollment
NCT04883073	Use of "Endo-App"	Other	Germany	Not yet recruiting	472
NCT03827174	Return to work coordination	Other, industry	Sweden	Unknown	160
NCT04109378	multidisciplinary surgery	Other	Hungary	Completed	150
NCT05831735	Physical activity and education	Other	France	Recruiting	150
NCT03994432	Mediterranean diet and physical activity	Other	Italy	Unknown	140
NCT05175248	Nutritional intervention	Other	United States	Recruiting	120
NCT05098444	Cognitive behavioral therapy	Other	Germany	Not yet recruiting	120
NCT05172492	Digital care at home	Industry	France	Recruiting	120
NCT04179149	Multi-level integrative medicine model	Industry, other	Puerto Rico	Recruiting	120
NCT04259788	AHEI diet	Other, NIH	United States	Recruiting	100
NCT04448366	Cognitive behavioral therapy	Other	Netherlands	Recruiting	100
NCT04711408	Virtual reality	Other	Israel	Recruiting	100
NCT05680350	Micro RNAs	Other	Egypt	Completed	100

Abbreviations: RCTs, Randomized controlled trials; APP, application; AHEI, Alternative Healthy Eating Index; NIH, National Institutes of Health.

In addition to delineating the evolving pattern, we also aimed to analyze the application, execution, and reporting of interdisciplinary trials on endometriosis. In comparison to projects focused on a single scientific field, interdisciplinary research has consistently encountered more challenges, such as greater difficulty in securing financial support.[55] We hypothesized that interdisciplinary trials on endometriosis might have a higher likelihood of premature termination due to financial constraints. However, the analysis did not substantiate the hypothesis. There has been a notable increase in registered interdisciplinary trials, with most actively advancing, and the majority of funding comes from non-industry sources. Through collaborative efforts of academic associations and policymakers, research funding for endometriosis has increased, attracting participation from researchers with diverse disciplinary backgrounds.[2] But there are still some concerns. Firstly, interdisciplinary trials are more likely to show some negative design characteristics, such as small sample size, single center-based, non-randomization, and unblindedness. These findings suggest that we are still in the early stage of development. Secondly, transparency concerns and lack of result reporting have persistently prevailed in endometriosis clinical trials,[56] and it is even worse in interdisciplinary studies. Interdisciplinary trials are less likely to provide results and keep updated in the database, potentially attributed to communication gaps among collaborators. In addition, a significant portion of completed trials did not reach publication. This may be attributed to inadequate study design, leading to trials ending with non-completion or negative results, or an extended research timeline required beyond initial projections for the integration of diverse disciplines. Meanwhile, the publication of interdisciplinary studies may face challenges due to the misalignment with the standards of discipline-specific journals. Thirdly, there is an unequal representation of different regions and demographic groups worldwide. Facilitating and investigating the delivery of care[57] will benefit more endometriosis patients while conducting research across diverse populations[58] contributes to enhancing the generalizability of results and gaining a more comprehensive understanding of this highly heterogeneous and genetically associated disease.[49]

Due to the limited representation of studies from Oceania in ClinicalTrials.gov, we conducted additional search in the Australian New Zealand Clinical Trials Registry (ANZCTR) and identified 68 trials on endometriosis, of which 16 were also registered in ClinicalTrials.gov. Consistently, we noted a significant increase in interdisciplinary studies covering clinical management and experimentation. But there was a higher proportion of studies reaching publication, including recent findings in supportive care,[59] Chinese herbal medicine,[60] and acupuncture.[40] They are mostly RCTs and/or have enrollments of at least close to 100, revealing the importance of rigorous research design and suggesting that trials on non-pharmacological interventions may require a relatively large sample size to identify the treatment effect.

In summary, well-designed randomized controlled trials are pivotal for advancing clinical practice. Our study innovatively offers evidence and insights into the current landscape of interdisciplinary clinical trials on endometriosis. The development is underway and accelerating, but a substantial path lies ahead fraught with challenges. For clinical trial investigators, facilitating multidisciplinary collaboration among clinicians, supportive care providers, biochemists, and statisticians, improving the process of trial design and execution, as well as promptly and objectively reporting results, will contribute to generating higher-quality clinical evidence and benefiting a larger population affected by this chronic systemic disease.

Limitations of the study

Our study still has some limitations. Firstly, the study was based on the analysis of a single database, ClinicalTrials.gov, and there are studies registered in other publicly available registries, as well as unregistered trials. The overall differences between the registries could potentially lead to false positive results, and we searched other clinical registries for discussion, such as those in Asia and Australia. Secondly, we did not include observational studies for analysis due to the difference in the calculation of sample sizes. Thirdly, though the identification of

interdisciplinary trials and all characteristics were independently checked by two authors, potential mistakes and disputes may still arise due to various factors, such as the different linguistic expression habits among trial investigators. Despite the limitations, our analysis based on ClinicalTrials.gov provides new evidence on the development and challenges of interdisciplinary clinical research on endometriosis from a novel perspective. The findings may contribute to fostering greater collaboration and provide valuable information for future investigators.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.109298.

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AUTHOR CONTRIBUTIONS

S.Z., F.F., and Y.X. initiated this study; Y.X. and Z.D. conducted the analysis and drafted the initial manuscript; S.Z., Y.X., and F.F. refined the analysis and revised the initial manuscript. All authors contributed to the final version.

DECLARATION OF INTERESTS

The authors declare no competing interest.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
ClinicalTrials.gov registry	The endometriosis trials were identified using the advanced search function of ClinicalTrials.gov, with the search queries "endometriosis OR endometrioses OR endometrioma" for "disease or condition".	https://clinicaltrials.gov/

RESOURCE AVAILABILITY

Lead contact

Additional details can be acquired by reaching out to the Lead Contact, Shengtao Zhou (shengtaozhou@scu.edu.cn).

Materials availability

All the clinical trials involved in this study are openly accessible in the clinical trial registry ClinicalTrials.gov. More details of the analyses are available upon request from Dr. Shengtao Zhou.

Data and code availability

- All data of the clinical trials included in this paper are accessible in the public registry ClinicalTrials.gov, and the study does not contain new primary experiment or clinical data.
- This study does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact, Shengtao Zhou (shengtaozhou@scu.edu.cn) upon request.

METHOD DETAILS

Creation of the trial subset

We performed a comprehensive analysis of the clinical trials on endometriosis in ClinicalTrials.gov database. The trials were identified using the advanced search function of ClinicalTrials.gov, with the search queries "endometriosis OR endometrioses OR endometrioma" for "disease or condition". The 2 additional words: "endometrioses" and "endometrioma" referred to the entry terms under the Endometriosis item in Medical Subject Headings (MeSH) database, provided by the National Center for Biotechnology Information (NCBI). With the XML download function, all available columns of the identified studies were downloaded from the registry to create a data subset for further manual screening. All interventional studies (clinical trials) working on diagnosis and management of endometriosis or pertaining to explore the occurrence and development of the disease were eligible for inclusion. Investigations with other indications such as adenomyosis and unexplained infertility were allowed, but endometriosis must be clearly stated in the condition column or the detailed page. All the preclinical studies (such as humanized animal models) and observational studies were excluded.

Variables and data extraction

Three types of variables were involved in this study. The following 12 columns could be directly downloaded from the database, including NCT Number (database identifier), title, status, sponsor, phases, enrollment, age, allocation, intervention model, start date, primary completion date and locations. Some variables were obtained through data processing of the downloaded information, such as follow-up duration and location type. Additional variables such as number of arms, outcome classifications, research topics and disease subtypes were obtained by manual data extraction from the trial record detail page. The outcome measures were categorized from both the titles and the descriptions of the endpoint section of the records, based on previous investigations[61] and relevant core outcome sets.[62]

The classification of trial topics was preliminarily collected based on the intervention type of the trials, then organized and summarized according to high-quality reviews[2,38] and recent clinical guidelines,[23] with further inquiries through public medical literature database (such as PubMed) for specific developing interventions. In addition, some trials were designed to collect biological and/or clinical information on endometriosis, focusing on investigating disease process and related molecular mechanisms. Different from traditional trials with the main purpose to evaluate specific interventions, these trials were identified as exploratory research. Relevant publications were retrieved from

public medical literature databases based on the registry identifier number. Although it is not mandatory at the time of trial publication, it reflects the overall situation and sponsors' names were also searched additionally to find the reporting of interdisciplinary trials.

Data extraction was performed independently by two investigators, with discrepancies resolved in consultation with a third senior gynecologist. The standardized forms were piloted within the top 30 trials and continued to be refined when necessary. The preliminary search started in January 2023, and the information (both downloaded or manually entered) was last updated and finalized in June 2023.

Identification of the interdisciplinary trials

The following studies were considered as interdisciplinary trials:

Trials with sponsors and/or collaborators who are not obstetrician-gynecologists, including other clinical practitioners, imaging experts, physical therapists, psychotherapists, primary healthcare providers, biochemists, and others.

Trials with interventions other than conventional obstetrician-gynecologist medical interventions, such as hormone therapy, surgery, non-hormone drug therapy, and assisted reproductive technology (ART).

Trials conducted in collaboration between clinicians and basic scientists, such as exploratory studies and assessments of biomedical engineering therapy. However, it is noteworthy that studies involving biologic therapy (such as monoclonal antibody) sponsored by pharmaceutical companies and conducted within obstetrics and gynecology were not considered interdisciplinary trials. This is because clinicians generally do not directly engage in the initial research and development process, and there is no direct collaboration with the basic scientists.

The identification process was conducted independently by two investigators, with discrepancies resolved in consultation with a third senior gynecologist.

QUANTIFICATION AND STATISTICAL ANALYSIS

Qualitative data were shown as frequency with percentage, while quantitative data were shown as median with interquartile range. The Pearson $\chi 2$ test or the Fisher exact test was used for the comparison of categorical variables, and the Wilcoxon rank-sum test was used for the comparison of quantitative variables (with unknown distribution or non-normal distribution). The criterion for statistical significance was 2-sided $P < 0.05$. Missing values were not included in analysis unless it could be manually retrieved from the trial detail page. Microsoft Excel was used for data collection, and R Studio (version 4.1.0) was used for data analysis and visualization.