To what end-point? Exploring clinical outcome assessments of pain in phase 2 and 3 trials and drug labels in women's health conditions

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BACKGROUND AND AIMS

- **Pain is a prevalent and debilitating symptom** across women's health conditions, **negatively impacting health-related quality of life** (**HRQoL**) and psychological functioning.[1-4]
- This review examined **how pain is assessed in clinical trials in select women's health conditions**, with a focus on exploring the **prioritisation** of pain within endpoint hierarchies, **methods of assessing pain**, and existing drug labels in women's health referencing the **treatment of pain**.

METHODS

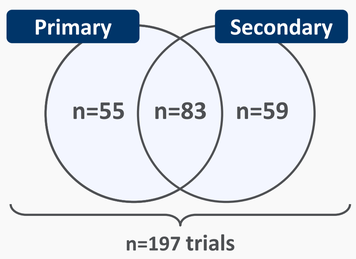
- The **ClinicalTrials.gov** database was searched to identify **Phase 2 and 3 interventional trials** in select women's health conditions using the database's search function to combine the following terms using the Boolean operator 'OR': **dysmenorrhea**, **endometriosis**, **polycystic ovarian syndrome** (**PCOS**), **uterine fibroids**, **ovarian cysts** and **menorrhagia**.
- Product labelling claims for pain treatments in women's health conditions were collected from the **Drugs@FDA** database.
- Treatments were identified for each condition, product information obtained, and labels reviewed for **pain-related language**.
- Searches were conducted in June 2025, with an updated search conducted in October 2025 (during poster preparation) yielding no additional records. Data on **trial design**, **intervention**, **indication/s**, **endpoints**, **clinical outcome assessments** (**COAs**) and **label content related to COAs** were extracted and reviewed.

RESULTS

Trial endpoints

- A total of 535 clinical trial records were identified. **Endometriosis trials were most frequent** (n=151/535, 28.2%), followed by **fibroids** (n=75/535, 14.0%) and **dysmenorrhoea** (n=55/535, 10.3%).
- **Fewer than half of the trials** specifically referenced 'pain' in primary, secondary or 'other' endpoint wording (n=204/535, 38.1%; Figure 1).

One trial was excluded during full review as although pain was mentioned in the endpoint, the symptom was only used as a criterion for post-operative morphine administration rather than as an endpoint. Final counts are based on n=204 trials.



'Other' endpoints (n=7)

Pain was also referenced in 'Other' endpoints:

- *n=2 also included pain in primary and secondary endpoints*
- *n=2 also included assessment of pain in the primary endpoint*
- *n=3 only included pain assessment in the 'Other' endpoints*

Figure 1. Positioning of 'pain' within the endpoint hierarchy of reviewed trials (n=204)

- The **most frequently assessed pain types** in primary/secondary endpoints were dysmenorrhoea and dyspareunia (Figure 2).
- Both were **most frequently** assessed as **secondary endpoints**.
- The three **conditions where pain was most frequently preceded by another symptom** in the endpoint hierarchy were uterine fibroids/leiomyomas, endometriosis and menorrhagia.
- Symptoms preceding pain included, e.g., **menstrual blood loss and hormonal changes** (Figure 3).

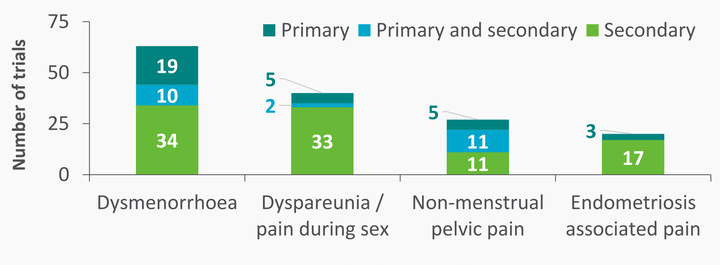


Figure 2. Most frequent pain types in reviewed primary and secondary endpoints (≥20 trials)

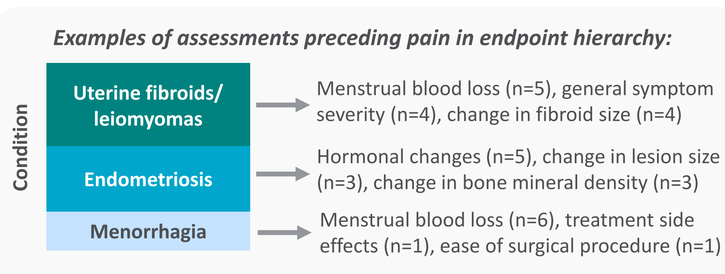


Figure 3. Symptoms preceding pain in endpoint hierarchy

Assessments of pain

- Across reviewed trials, **31 named COAs** used to assess pain were identified.
- Additionally, there were **78 instances where a specific COA was not named** but a non-specific COA description was included (e.g., NRS, VAS, 'diary').
- Across the reviewed trials, pain was **most frequently assessed** using **NRS** (n=163) or **VAS** (n=97) items (Figure 4).
- As expected, most COAs used to assess pain were **PROs** (n=29); n=2 were combined **PRO/ClinROs** (clinician-reported outcome).
- Most reviewed assessments used COAs that were **pain-specific but not disease-specific** (n=190).
- Only **n=26** of the reviewed assessments were specific to **both pain and the disease area/condition** (Table 1).

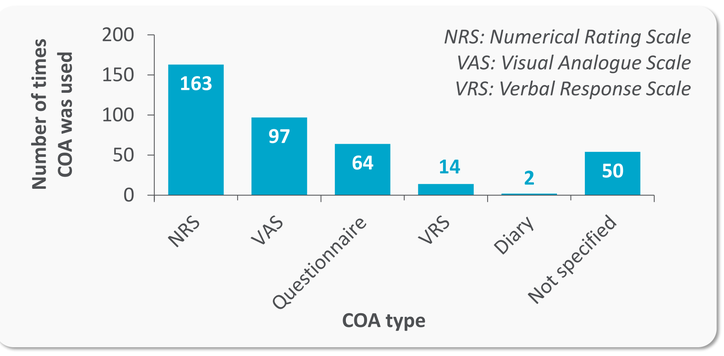


Figure 4. COA types used to assess pain across reviewed trials (n=204)
All trials included >1 COA assessment, each COA was counted only once per trial. Each type of NRS/VAS/VRS was counted separately within and between trials.

Table 1. Specificity of COAs to pain and/or disease area

Specificity	Disease-specific[a]	Not disease-specific[b]
Pain-specific	n=26	n=190
Not pain-specific	n=67	-

[a]For example, established COA in disease area, disease-specific NRS;
[b]For example, generic COA, generic NRS (assessing a non-disease specific symptom); Sufficient information to characterise the COA was not available (n=107).

Biberoglu and Behrman (B&B) scale[5]
PRO & ClinRO
n=27

Endometriosis Health Profile-30 (EHP-30)[6]
PRO
n=23

Composite Pelvic Signs and Symptoms Score (CPSSS)[7]
PRO & ClinRO*
n=9

Brief Pain Inventory (BPI)[8]
PRO
n=7

**CPSSS is a modified version of the Biberoglu and Behrman (B&B) Scale.*

Figure 5. Most frequently identified named COAs used to assess pain across reviewed trials (n=204)

- The named COAs used most frequently to assess pain were: **B&B scale**, **EHP-30**, **CPSSS** and **BPI** (Figure 5).
- The **most frequent pain types assessed by the COAs** were dyspareunia, pelvic pain/tenderness, dysmenorrhoea, non-menstrual pelvic pain and endometriosis-associated pain.
- Dysmenorrhoea, dyspareunia and pelvic pain/tenderness were assessed by both the **B&B scale** and **CPSSS**. The **EHP-30** was only used to assess **endometriosis-related pain**. Although generic, the **BPI** was not always used in conjunction with a **disease-specific measure**.
- Out of these COAs, only the **EHP-30** was **developed with input from patients in the target population** and has strong evidence supporting its validation.[6]

Drug labels

- In the past 15 years, **FDA-approvals for two drugs for pain associated with a women's health condition** were identified – both for endometriosis (Table 2).
- A combination of **disease-specific and generic COAs** were included in both ORILISSA® and MYFEMBREE® trials.[9-12] Ultimately, **standalone pain NRS items** and **disease-specific HRQoL assessments** resulted in **label claims**.[13-14]
- Other drugs for pain were approved **prior to the 2009 FDA PRO guidance** or for conditions also affecting those assigned male at birth (e.g., SAVELLA® to treat fibromyalgia).

Table 2. COA endpoints in ORILISSA® and MYFEMBREE® Phase 3 trials

COA / Drug	Pain NRS items	EHP-30	Endometriosis Daily Pain Impact Scale	B&B scale	Generic HRQoL COAs	PGI-C	CPSSS	Patient Global Assessment
ORILISSA® (elagolix)	✓+ overall endometriosis-associated pain	✓+ pain domain, sexual intercourse domain	✓ dysmenorrhoea and non-menstrual pelvic pain *+, dyspareunia+	-	✓+ EQ-5D-5L, HRPQ	✓+ endometriosis-associated pain	*Used for screening only*	-
MYFEMBREE® (relugolix, estradiol and norethindrone acetate)	✓ dysmenorrhoea and non-menstrual pelvic pain *+ dyspareunia+	✓+ pain domains	-	✓+ functional impairments: dysmenorrhoea, non-menstrual pelvic pain, dyspareunia	✓+ EQ-5D-5L	✓+ dysmenorrhoea, non-menstrual pelvic pain, dyspareunia	-	✓+ dysmenorrhoea, non-menstrual pelvic pain
	✓+ overall pelvic pain	✓+ non-pain domains						

*primary/co-primary endpoints | +secondary endpoints | : COA results in label | **EQ-5D-5L**: European Quality Of Life Five Dimension Five Level | **HRPQ**: Health Related Productivity Questionnaire

CONCLUSIONS AND RECOMMENDATIONS

Although several trials in women's health conditions were identified, particularly for endometriosis, fibroids and dysmenorrhoea, **less than half of the trials included pain in the endpoint hierarchy**.

Trials that included pain within the endpoint hierarchy, most frequently included pain assessments within both **primary and secondary endpoints** (n=83).

Pain was most typically assessed using a **generic**, **single-item COA** (e.g., NRS or VAS) rather than a disease-specific, validated PRO instrument, **highlighting a potential gap in tailored**, **in-depth patient-centered assessments**. Of the disease-specific COAs that were identified, most were endometriosis-specific (i.e., **B&B Scale**, **EHP-30**).

Only **two drugs have received FDA approval for pain associated with women's health conditions**, both indicated for **endometriosis**. COAs, especially pain NRS items, were included as primary and secondary endpoints, and cited in final product labelling.

- **Relevance**: Pain is a prevalent and debilitating symptom across women's health conditions; however, pain was not referenced in trial endpoints as consistently as expected. Aligning future COA development with FDA Patient-Focused Drug Development (PFDD) and COA Compendium guidance would ensure that endpoints are relevant to the patient experience, conceptually sound and in line with regulatory guidance.
- **Recommendations**: Previously incorporated endpoints and existing COAs can capture pain but may all not fully reflect the symptom's complex nature. Including disease-specific, multi-item COAs could enhance and enrich the depth of PRO data collected for pain in women's health conditions beyond the capabilities of single-item scales.

References:

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