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Rethinking Women's Health - Unpacking the 2024 Women's Health Research Roadmap with A Landscape Review of Clinical Outcome Assessments (COA), Health Agency Recommendations and Drug Label Claims with COA Related to Women's Health

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Background

The **women's health (WH) gap** remains **a critical issue** in the 2020s[1,2]. Women spend **25% more of their lives** in **debilitating health** than men[3]. To help bridge the women's health (WH) gap, the **FDA's WH Office updated** their **Research Roadmap in 2024**[4,5]. Selecting **appropriate clinical outcome assessments (COAs)** and **endpoints** was cited once more as a **key priority area**. In our previous WH study we reviewed COAs developed in a female population and their use in labels and guidelines.

Objective

To **explore** the **WH COA landscape** by identifying COA availability, as well as their presence in regulatory guidance and drug label claims.

Methods

1. **Roadmap recommended therapeutic areas mapped to Medical Subject Heading therapeutic indications**
2. **Searched MeSH therapeutic indications within[6]:**
   - PROQOLID™ (Clinical Outcome Assessments Database) → **Clinical Outcome Assessment**
   - PROINSIGHT™ (Providing Regulatory Insights to Clinical Outcome Assessments) → **Health agency guidelines***
   - PROLABELS™ (Clinical Outcome Labeling Claims Database) → **Approved drug and device labelling claims***

*With COA

Main Outcomes

- **527 COAs** were identified which covered **254** different **therapeutic indications. 9%** (n=47) were developed in an **all-female population**
- Lowest number of COAs for **cardiovascular diseases** (n=12 COAs, 2%), **psychological phenomena** (n=23 COAs, 4%), and **musculoskeletal diseases** (n=26 COAs, 5%)
- **21 guidelines** identified including **9 COAs** – **none** of which were developed in an **all-female population**
- **106 labels** encompassing **48 COAs** (**8** of which were developed in an **all-female population**)
- **FDA** have **approved more labels** in these therapeutic areas **since 2015** than the EMA, but there are **more COAs** in EMA approved labels than FDA labels

Future Direction

- Further research into **cardiovascular** and **musculoskeletal diseases,** and **psychological phenomena**
- Remains a need to **develop COAs** with women which are **specific for women's health needs**
- **Need for more guidance** on how to **capture women's health needs** in COA measurement
- More COAs **developed for women** to be used in **labels** targeting WH priority **therapeutic areas**

Results

PROQOLID™ (Clinical Outcome Assessments Database)

PROQLID was searched by therapeutic indications corresponding to the Roadmap's recommended therapeutic areas to prioritise for WH. This retrieved **527 COAs** covering **254 different therapeutic** indications. **47** of the **527 COAs** identified were developed in an all-female population.

Therapeutic Areas

Greatest Number of COAs	Least Number of COAs
Neoplasms (n=267 COAs, 51%) • 11% (n=30) in an all-female development population • 50% were (n=15) for breast neoplasms	**Cardiovascular diseases** (n=12 COAs, 2%) • 0 in all-female development population
Diabetes (n=118 COAs, 22%) • 0 in all-female development population	**Psychological phenomena** (n=23 COAs, 4%) • 4% (n=1) in an all-female development population for body image in women with breast cancer
Substance-related disorders (n=53, 10%) • 0 in all-female development population	**Musculoskeletal diseases** (n=26 COAs, 5%) • 34% (n=9) in an all-female development population • All-female COAs were for osteoporosis with 4 specifically for post-menopausal osteoporosis

Discussion: These findings are in line with several reports showing that breast cancer research receives the greatest amount of funding compared to other cancers in the UK[9] and USA[10]. Further, there is a shortage of COAs developed with a WH focus being used in key therapeutic areas. It is important to address this difference as research shows women have **different health experiences** to men and **disease can manifest differently** in men to women[3].

Concept of Interest

Most common concept measured (total n=227 COAs)

Health-Related Quality of Life

- Non-female specific developed COAs: **42%** (n=201)
- All-female developed COAs: **55%** (n=26)

No other remarkable differences between the concept related to female development population. Although the **variety** of other **concepts** measured was **marginally greater** for the non-female specific COAs, e.g. health-related quality end of life, utility, and other.

The top **therapeutic areas** for which HRQoL was measured:

- Neoplasms (n=19)
- Osteoporosis (n=7)

→ All-female population

- Neoplasms (n=133)
- Diabetes (n=45)

→ Non-female specific population

One reason why there are slightly more COAs developed in an all-female population measuring HRQoL may be because some studies have found that women tend to report lower HRQoL compared to men[8] and so it is important to ensure that COAs are fit-for-women.

Type of COA

472 PROs | **21 ClinRO** | **10 Composite** | **10 ObsRO**

16 COAs were also available as different types of COAs, e.g. either a PRO or an ObsRO, PRO or a ClinRO

- **89%** (n=425) of COAs not developed in a female-specific population were PROs
- **All** COAs developed in an all-female population were PROs.

Researchers who are consciously developing COAs with an all-female population may be acutely aware of the **importance of eliciting women's perspective** when measuring health outcomes due to their **historical absence from health research**[7].

PROINSIGHT™ (Providing Regulatory Insights to Clinical Outcome Assessments)

PROINSIGHT was searched by therapeutic indications corresponding to the Roadmap's recommended therapeutic areas to prioritise for WH. This retrieved **21 guidelines** including **9 COAs.** To facilitate in-depth analysis and comparison with PROLABELS we focused on the **FDA** and **EMA** who published **6** and **5** guidelines with COAs respectively, covering **6 named COAs** across **6 endpoints and 13 therapeutic indications**. **None** of the **named recommended COAs** were developed in an **all-female population.**

Therapeutic Areas

The EMA and FDA were fairly **aligned** on issuing guidelines in similar **therapeutic areas**. Most common therapeutic areas were **obesity** (EMA= 2; FDA= 1 guideline), **chemotherapy-induced nausea and vomiting** (CINV) (EMA=2; FDA=1 guideline), as well as two guidelines from the EMA on **diabetes**. Both agencies also aligned on therapeutic areas in which **specific COAs had been named** for **CINV** (EMA=2; FDA=5 named COAs) and **neoplasms** as well for the FDA (1 named COA). The focus on these therapeutic areas was also **reflected** in **COA** and **drug label data.**

Endpoint Positioning with COA

There were **differences** between the agency in **endpoint positioning**. **EMA** recommended **more primary** and **secondary endpoints with COA** recommendations (n=3 and n=7 endpoints respectively) compared to FDA (n=3 and n=2 endpoints respectively). However, **FDA and EMA** recommended the same number of **not specified endpoints with COA** (n=9). Notably, **FDA** specifically **named 5 COAs** for not specified endpoint use whereas the EMA only **named 1 COA** for a secondary endpoint, highlighting a **shortage of named COAs for endpoints with COA recommendations**.

Type of COA Recommended

	EMA	FDA
PROs	n=17	n=9
ClinROs	n=1	n=0
Composite	n=0	n=2
PerfOs	n=1	n=0
ObsROs	n=0	n=0
Unspecified	n=0	n=3

Concept of Interest
HRQoL uniquely measured by PROs, **Fracture incidence** by ClinROs, **Exercise** by PerfO

FDA:
- PROMIS Item Bank v1.0 – Severity of Substance Use
- EORTC-QLQ-C30
- PRO-CTCAE
- NSCLC-SAQ
- FACIT

EMA:
- Functional Living Index - Emesis

Guideline Publication over Time

One **more guideline published** between **2015-2024 (n=6 guidelines)** in comparison to **2005-2014 (n=5 guidelines):**
- **2004-2014: EMA** issued **4 of 5** guidelines published in this period
- **2015-2024: FDA** issued **5 of 6** guidelines published in this period

This fits with the broader trend and may not be linked to the WH Roadmap:
- **2004-2014: EMA** (n=34 guidelines) **published more guidelines with COA** recommendations than the FDA (n=15 guidelines)
- **2015-2024: FDA** (n=91 guidelines) **published more guidelines with COA** recommendations than the EMA (n=36 guidelines)

Guidance on Women's Health Needs

Limited consideration of how prevalence of these therapeutic areas and/or how they may manifest differently in women was seen in the guidelines.

Fits with broader literature highlighting the lack of specific guidance on women's unique health needs with a consideration of how experiences may differ from men[11].

EMA - Main consideration for:
- **CINV**: women are at higher risk of CINV and recommended this be reflected in clinical trial populations
- **Osteoporosis**: discussion of how the disease manifests differently in women -explicit focus on postmenopausal women

FDA - Main consideration for:
- **CINV**: suggested that female sex to be adjusted for in statistical analysis as this can impact efficacy outcomes.
- **HIV**: consideration for trials in pregnant and/or high-risk women because determination because of the variable historical evidence of HIV prevention efficacy in at-risk women.

PROLABELS™ (Clinical Outcome Labeling Claims Database)

PROLABELS was searched by therapeutic indications corresponding to the Roadmap's recommended therapeutic areas to prioritise for WH. This retrieved **106 labels** encompassing **48 named COAs** across **99 endpoints** and for **39 therapeutic indications. 8 COAs** used were developed in an **all-female population**.

Therapeutic Areas

Most Common Therapeutic Areas	Least Common Therapeutic Areas
Osteoporosis (n=30 labels; FDA=17/EMA=13)	**Cardiovascular disease** (n=1 label FDA)
Breast neoplasms (n=25 labels; FDA=12/EMA=13)	**Autoimmune diseases** (n=1 label EMA)
Diabetes (n=24 labels; FDA=15/EMA=9)	**HIV Infections** (n=1 label FDA)

COAs developed in a female-specific population: **1** for **postmenopausal osteoporosis** and **3** for **breast neoplasms**

Endpoint Positioning

Distribution of endpoint positioning with COAs:
- Primary endpoints: n=77 COAs
- Secondary endpoints: n=113 COAs
- Tertiary/Exploratory endpoints: n=4 COAs

5 COAs developed in a female-specific population were for **secondary** endpoints, **1** was **exploratory**, **4** were **not specified**

Common COAs for **FDA** primary endpoints:
- *Memorial Pain Assessment Card* (pain intensity) (n=4 endpoints)
- *Karnofsky Performance Status* (performance status) (n=4 endpoints)

EMA only had **one label** with a named COA used to measure a primary endpoint: *Severity Weighted Assessment Tool* (complete response)

Endpoints were largely measured by **PROs** (n=104) compared to **ClinROs** (n=72) or **composite** (n=48)

Concept of Interest

Most common concepts measured by specific COAs

Pain

Pain was measured by COAs for **6 FDA** and **5 EMA** label endpoints

Pain most frequently measured by:
- **EMA**: EORTC QLQ-C30 (2 endpoints) and Brief Pain Inventory (2 endpoints)
- **FDA**: Memorial Pain Assessment Card (n=4 endpoints)

Health-Related Quality of Life

HRQoL was measured by COAs for **12 FDA** and **31 EMA** label endpoints

HRQoL most frequently measured by:
- **EMA**: EORTC-QLQ-C30 (n=9 endpoints)
- **FDA**: SF-36 Health Survey (n=5 endpoints)

6 of the **8** COAs developed in a female-specific population measured **HRQoL**

Drug Approval and COA Use

- Slightly more labels were approved between **2015-2024 (n=42 labels)** than **2005-2014 (n=38 labels)**
- Since 2015, a slightly **more labels** have been **approved** by the **FDA (n=22 labels)** than the **EMA (n=20 labels)**
- **More COAs have been used** in **2015-2024 (n=48 COAs)** versus **2005-2014 (n=32)**. This increase in COA use is mainly due to **EMA labels (n=29 COAs)** than **FDA (n=19 COAs).** However, only **3 female-specific COAs** have been used since **2015** vs **9 pre-2015.**

Label approvals **reflect the guidelines** regarding most common **therapeutic areas**, but we see **more primary endpoints with COA** than secondary and tertiary - a **difference** to the guidelines. As with guidelines, there has been an **increase in labels** published in the last 10 years although the agency split is more equal – even if the **presence of COAs** in labels per agency is not.

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