# Translating Pain

## 1. What are you trying to do?

What if women's pelvic pain were measured as precisely as blood pressure?

Chronic pain is one of the largest unsolved health problems in the world. In the United States alone, it costs an estimated $722 billion each year in medical care and lost productivity.[1] Within that, chronic pelvic pain in women accounts for more than $150 billion annually, affecting nearly 1 in 7 women, disrupting work, education, fertility and daily life.[2,3]

Today, pain is still captured by questionnaires and 0 to 10 scales.[4] These tools matter, because the patient's experience is what counts, but they do not tell us what is happening in the uterus, pelvis or nervous system, leaving drug developers with no biologically precise way to see or predict the nuances of pain in individual women. This programme therefore asks:

**Can we discover and clinically validate composite non-invasive markers of pelvic pain types in diseases like endometriosis, rather than relying solely on subjective surveys?**

Translating Pain is an innovation programme that runs a single, closed-loop test to develop quantitative measures of women's chronic pelvic pain types. Over four years we will combine neurophysiology with non-invasive biofluid assays, identify a composite biomarker, validate it prospectively in patients and preclinical models, then evaluate it in a clinical trial.

By programme end, we submit a non-invasive pelvic pain measurement tool to MHRA as a predictive stratifier for Phase 2 endometriosis or adenomyosis trials in a defined context of use, and establish a regulatory playbook for composite pain biomarkers for diseases where structure and pain are uncoupled.

## 2. How is it done today, and what are the limitations?

Women with chronic pelvic pain are still asked to rate their pain on simple questionnaires. For endometriosis and adenomyosis, these pain scores are often the primary measure of drug success. Structural changes on imaging or at surgery often do not correlate with pain relief; a uterus that looks "better" can still belong to a patient who lives with debilitating pain.[5,6] Existing tools and programme technical domains include:

**Neurophysiology–**EEG and fMRI are increasingly available and have shown signals in women with endometriosis-related pain,[7,8] but most studies are small and do not combine neuroimaging with omics in women's pelvic pain. To date, there are no regulator-facing testbeds where neurophysiology, biofluids and patient surveys (PROMs) are collected together under harmonised protocols.

**Molecular tools–**No single biofluid marker reliably separates chronic pain types, while multi-marker, multimodal approaches have shown more promise.[9] Epigenetic and multi-omic work is revealing molecular subtypes of endometriosis and related conditions,[10,11] and high-throughput biomarker platforms already exist and are technically robust, but commercial pressures steer them toward larger fertility markets. Translating Pain will apply existing assays to identify molecular predictors of pelvic pain types in combination with neurophysiology.

**Preclinical models–**Rodent endometriosis models generate ectopic lesions and inflammation,[12] but standard lab mice do not menstruate. Improved models, including menstruating rodents,[13] show pain phenotypes during menses. *In vitro* systems capture structural, hormonal and inflammatory pathways but not structure and pain together.[14] Translating Pain will fund development of pain phenotypes in pre-established structural models that link to programme's pain biomarkers to improve predictive validity.

**Regulatory and coordination gaps–**Initiatives like NIH HEAL and IMI-PainCare have standardised elements of chronic pelvic pain research and created composite surveys,[15,16] but they have not been clinically validated for women's chronic pelvic pain, or are weakly tied to preclinical models. The field

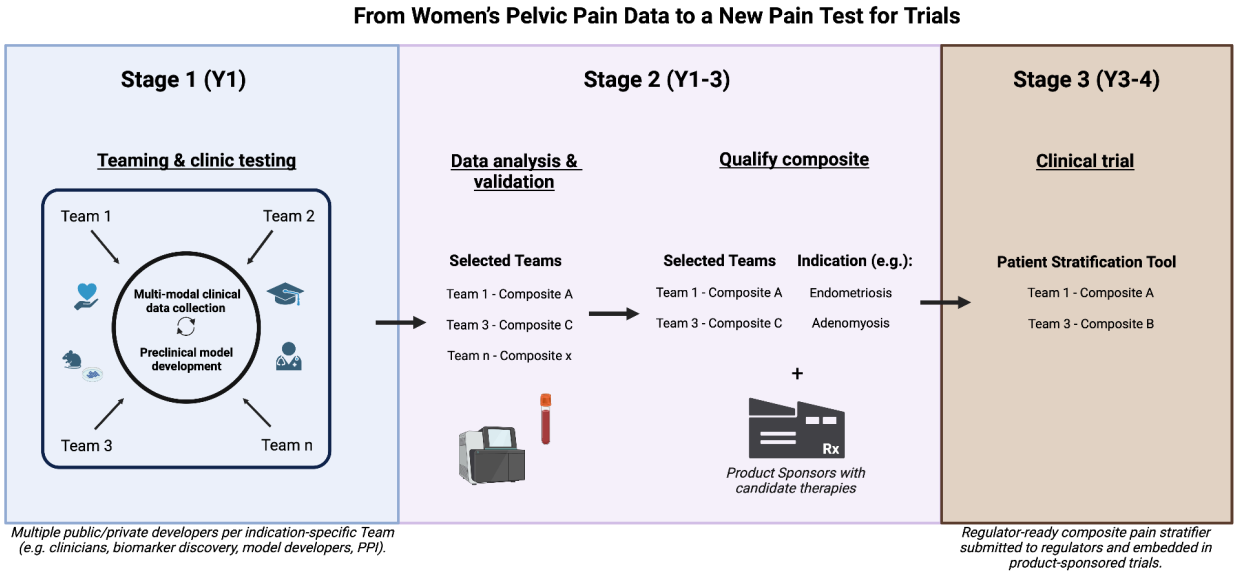
has pieces of the solution but not a coordinated regulator-facing programme that combines neurophysiology, molecular assays, and models for women's pelvic pain disease. Translating Pain is designed to close that gap.

### 3. What is new about your approach, and why do you think it will be successful?

This is a single, time-bound test to discover, validate and hand over a composite pelvic pain biomarker as a prespecified patient stratifier for a specific context of use, rather than an open-ended effort to "study pelvic pain". It focuses on women's pelvic pain where structure-pain discordance is severe and clinical need is acute, while building a template that can be reused for other chronic pain diseases.

The programme creates public-private, pre-competitive, clinically facing teams that combine NHS clinics, academic clinician-scientists, biomarker and device companies, preclinical model developers and patient and public involvement partners under unified governance.

Teams span the programme's core technical domains and will compete through three Stages in an ARPA Challenge format. Starting with about 5 teams (Stage 1), they are down-selected to 2-3 teams (Stage 2), and 1-2 teams finish (Stage 3). The final composite biomarker must add predictive lift over PROMs, maintain performance in new cohorts and sites, improve trial efficiency when used as a prespecified stratifier, and fit within realistic clinical workflow and cost.




- **Stage 1 (0 to 18 months):** Establish a shared NHS testbed and governance, lock the supervisory label (PROMs and pain diary), deploy clinic-feasible neurophysiology and biofluid collection, and show that multimodal signals are measurable and repeatable.
- **Stage 2 (12 to 42 months):** Analyse and validate composites on shared patient datasets and link them to preclinical models. Composites must show reproducible predictive lift over PROMs alone. Protocol and statistical analysis plan for Stage 3 are developed in parallel, and regulators are looped-in early to define context of use.
- **Stage 3 (36 to 48 months):** Initiate a clinical trial and embed the composite as a prespecified stratifier, confirming QC, workflow time and incremental cost, initiating recruitment with the drug product sponsor. Trial completion and later regulatory steps are owned by the sponsor.

### 4. Who cares? What difference will it make?

For women and clinicians, the programme aims to move from a vague label of "chronic pelvic pain" to biologically defined subtypes that guide precise therapeutic decisions. A composite biomarker may help distinguish inflammatory phenotypes, neuropathic features and nociplastic states[17,18] that currently have no clinical quantitative measurements. Quantitative tools for pain subtyping would support decisions about invasive surgery, hormonal therapies and allow more targeted treatments anchored to biology.[5,6]

For drug developers, a tool that identifies pain types would enable precise therapeutics that improve patient pain, not just imaging endpoints. Predictive preclinical models that faithfully capture both pain and structure, validated with this tool, would enable smaller, faster, successful clinical trials.[9,12]

For regulators, payers and the UK innovation system, reproducible endpoints that capture pain biology rather than structure alone would make the UK a more attractive place to develop chronic pain therapies. The programme will seed domestic capability in pain therapeutic translation beyond women's health conditions to impact many other chronic diseases with structure-pain discordance.[9,18]

## 5. What are the main risks, and how will they be managed?

**Modality integration risk–**Modalities have been used in isolation but not together in a regulator-facing programme. Staging, down-selection and a central technical integrator with harmonised SOPs and data models reduce this risk. **Data integration and quality risk–**Data from different sites, devices and assays may not be interoperable. A central integrator defines common data models, metadata standards and shared assay panels, and only features that meet predefined reliability thresholds enter the composite. **Regulatory and adoption risk–**Regulators or sponsors may want different evidence. The context of use and Target Development Profile will therefore be co-designed with MHRA early, with ILAP and written advice, and at least one sponsor agreement is required for Stage 3. NICE engagement aligns endpoints, and Teams are judged on prospective lift over PROMs rather than volume of exploratory signals.

## 6/7. How long will it take, and how much will it cost?

The programme costs £50M across four years, with an option to extend by up to 12 months for transition and handover. Stage 1 establishes the clinical testbed, harmonizes PROMs, and initiates preclinical and biomarker platform work. Stage 2 expands recruitment, refines and validates composites on shared datasets, patients, and preclinical models. Stage 3 embeds the stratifier in a UK therapeutic trial, activates sites and begins recruitment with the composite used as a prespecified stratifier alongside PROMs.

## 8. What are the mid-term and final exams?

**Final exam**

- At least one non-invasive composite pelvic pain biomarker accepted by MHRA as prespecified predictive stratifier for a UK Phase 2 endometriosis or adenomyosis trial, with >0.10 lift in AUC or $R^2$ over PROMs and performance maintained in an independent cohort and NHS site.
- The stratifier locked on a regulatory dataset of ≥600 women (≥300 post lock), run in ≥2 NHS sites with ≤60 minutes extra visit time and ≤£600 per patient, supported by ≥1 human-relevant models modulating key components.

**Mid-term exam**

- Shortlisted composites gain over PROMs in time-split or site-split validation; at least one meets test-retest and prospective thresholds with repeat tests within ≤15% and handling effects ≤10%.
- Early MHRA advice defines context of use and plan for Phase 2 stratifier use. ≥2 sponsors give written intent to embed the composite as a stratifier alongside PROMs in a UK Phase 2 trial.

If these conditions are met, Translating Pain will have shown that it is possible to move from subjective pain scores to a composite biomarker used prospectively in a regulated trial and will create a practical blueprint for tackling chronic pain more broadly.