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Strategic context:

Standardized Medical Name: Difficult-to-Treat Rheumatoid Arthritis (D2T RA)

Target Patient Profile:

- **Temporality:** Prevalent
- **Disease Stage/State:** Established, Active, and Multi-Drug Resistant/Refractory. Defined according to EULAR criteria: Failure of ≥2 biologic (bDMARDs) and/or targeted synthetic DMARDs (tsDMARDs) with different mechanisms of action (MOA), accompanied by signs of active/progressive disease (e.g., at least moderate disease activity, inability to taper glucocorticoids, or persistent symptoms impacting quality of life).

Strategic Rationale: Pharmaceutical Relevance (2025-2026):

Difficult-to-Treat Rheumatoid Arthritis (D2T RA) represents the central unmet medical need and the primary strategic focus for innovation within the RA landscape for the 2025-2026 horizon. The market is saturated with established mechanisms of action (e.g., TNF inhibitors, IL-6 inhibitors, JAK inhibitors, T/B-cell modulators). Consequently, the critical challenge—and the key opportunity for market differentiation—lies in the estimated 5-20% of patients who cycle through these advanced therapies without achieving sustained remission.

The industry's immediate agenda is driven by the necessity to manage this multi-refractory population, particularly patients who have failed both biologics and JAK inhibitors. Recognizing the diminishing returns of cycling existing therapies and the safety concerns surrounding long-term JAK inhibitor use, the R&D focus for 2025-2026 is squarely on validating and introducing novel MOAs and modalities capable of inducing remission where current advanced therapies have failed.

Key late-stage pipeline activities and market entries demonstrating this strategic imperative include:

- **Restoring Immune Homeostasis (PD-1 Agonism):** AnaptysBio is advancing Rosnilimab, a PD-1 agonist designed to deplete pathogenic T cells and restore immune balance. Positive Phase 2b (RENOIR trial) data reported throughout 2025 demonstrated "JAK-like efficacy," notably including strong responses in the b/tsDMARD-experienced population. Progression toward Phase 3 is anticipated in late 2025 or 2026.
- **Neuroimmune Modulation (Devices):** The D2T space is seeing the entry of entirely new modalities. SetPoint Medical received FDA approval in July 2025 for the SetPoint System (Vagus Nerve Stimulation). It is specifically indicated for moderate-to-severe RA patients with inadequate response or intolerance to b/tsDMARDs. Commercial

expansion is planned for late 2025 and early 2026, signaling a major shift in the refractory treatment paradigm.

- **Targeting Pathogenic Autoantibodies (FcRn Inhibition):** The role of FcRn inhibitors in reducing pathogenic IgG antibodies is being actively investigated. J&J's Nipocalimab has established proof of mechanism and is progressing into combination studies (e.g., DAISY-RA trial with anti-TNFs) targeting refractory populations. Immunovant is also aggressively advancing IMVT-1402, with plans to initiate multiple trials by early 2026, with RA being a key potential indication.
- **Emerging Cytokine Pathways (TL1A):** Investigation into alternative inflammatory drivers is accelerating. Spyre Therapeutics initiated the Phase 2 SKYWAY basket trial in September 2025, evaluating SPY072 (anti-TL1A) in rheumatic diseases including RA, with proof-of-concept data expected in 2026.
- **Immune Tolerance Induction:** Representing a strategic shift towards immune "resetting," the AuToDeCRA2 trial (Phase IIa), launched in March 2025, is investigating tolerogenic dendritic cell (tolDC) therapy, aiming for durable remission in refractory patients.

Intended Clinical Application Research Utility:

Epidemiological research characterizing the D2T RA population is essential to support the commercialization and market access strategies for novel therapies (e.g., PD-1 agonists, VNS, FcRn inhibitors) entering the saturated RA market in 2025-2026. The primary utility lies in quantifying the substantial clinical and economic burden, healthcare resource utilization (HCRU), and real-world treatment patterns (specifically the sequence, duration, and outcomes of advanced therapy cycling, including post-JAK failure). By demonstrating the inadequacy of the current standard of care in this multi-refractory population, this data is critical for Health Technology Assessments (HTA), payer negotiations, and designing comparative effectiveness research to justify the value proposition of new mechanisms.

Phenotype Description: Difficult-to-Treat Rheumatoid Arthritis (D2T RA)

1. Clinical Condition

Recommended Phenotype: Difficult-to-Treat Rheumatoid Arthritis (D2T RA)

Synonyms:

- Refractory Rheumatoid Arthritis
- Multi-drug resistant Rheumatoid Arthritis (MDR-RA)
- Treatment-refractory RA
- Severe, persistent RA

Note: While sometimes used interchangeably with "Severe RA," D2T RA specifically refers to the subset defined by treatment failure rather than overall disease severity alone.

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2. Detailed Presentation

Overview Difficult-to-Treat Rheumatoid Arthritis (D2T RA) describes a subset of patients with established rheumatoid arthritis (RA) characterized by persistent, active inflammation and failure to achieve treatment targets despite sequential use of advanced therapies with different mechanisms of action (MOA). This phenotype represents the central unmet medical need in the current RA landscape.

Clinical Presentation and Assessment Patients present with ongoing signs and symptoms of active RA, including persistent synovitis (joint swelling and tenderness), significant morning stiffness, fatigue, and polyarticular pain. Assessment relies on standardized composite measures of disease activity (e.g., DAS28-CRP/ESR, CDAI, SDAI), which consistently indicate moderate or high disease activity. Patient-reported outcomes frequently reflect significant functional impairment and diminished quality of life.

Diagnostic Criteria (EULAR Definition): The diagnosis requires a prior confirmed diagnosis of RA (e.g., meeting ACR/EULAR classification criteria). The consensus definition for D2T RA, established by EULAR, requires the presence of the following criteria:

1. **Treatment Failure:** Failure of at least two biologic DMARDs (bDMARDs) and/or targeted synthetic DMARDs (tsDMARDs) with different mechanisms of action, following failure of conventional synthetic DMARDs (csDMARDs) (unless contraindicated). Failure includes lack of efficacy (primary or secondary) or intolerance.
2. **Signs of Active/Progressive Disease:** Evidence of ongoing disease activity, such as:
    - At least moderate disease activity by validated composite measures.

- Elevated acute phase reactants (C-reactive protein [CRP], Erythrocyte Sedimentation Rate [ESR]).
- Inability to taper glucocorticoid doses below a certain threshold (e.g., 7.5mg prednisone equivalent/day).
- Evidence of rapid radiographic progression.

Laboratory Tests and Imaging: Laboratory findings typically include elevated CRP and ESR. Seropositivity (Rheumatoid Factor [RF], anti-citrullinated protein antibodies [ACPA]) is common but not required for the D2T definition. Imaging (ultrasound, MRI) is crucial for confirming persistent synovitis and distinguishing inflammatory activity from structural damage.

Treatment History and Medications (RWD Focus): Documentation of the treatment history is central to identifying this phenotype. Patients will have a documented history of inadequate response or intolerance across multiple classes:

- **csDMARDs:** e.g., methotrexate, leflunomide.
- **bDMARDs:** e.g., TNF inhibitors, IL-6 receptor inhibitors, T-cell costimulation modulators (abatacept), B-cell depletion therapy (rituximab).
- **tsDMARDs:** e.g., JAK inhibitors.

Management of D2T RA involves cycling through remaining advanced therapies or utilizing novel modalities, such as Vagus Nerve Stimulation (VNS) devices, and investigational agents targeting new pathways (e.g., PD-1 agonism, FcRn inhibition). Chronic reliance on glucocorticoids is common.

Differential Diagnoses and Comorbidities: It is critical to differentiate true inflammatory D2T RA from "pseudo-refractory" RA, where persistent symptoms are driven by non-inflammatory factors.

- **Differential Diagnoses:** Non-inflammatory pain syndromes (e.g., fibromyalgia), secondary osteoarthritis, or mechanical joint damage must be distinguished from active synovitis.
- **Comorbidities:** Patients have high rates of comorbidities, often exacerbated by chronic inflammation and long-term immunosuppression, including cardiovascular disease, serious infections, osteoporosis, and interstitial lung disease.

Prognosis and Complications: The prognosis for D2T RA is characterized by a high risk of irreversible joint damage, progressive disability, significant healthcare resource utilization, and increased mortality compared to the general RA population.

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3. Phenotype Boundaries and Granularity

This phenotype is narrowly defined to capture the multi-refractory population failing current advanced therapies, consistent with the EULAR definition.

General Exclusions The following clinical ideas are out of scope:

- Treatment-naïve or Early Rheumatoid Arthritis.
- RA adequately controlled by csDMARDs.
- RA adequately controlled by first- or second-line b/tsDMARDs.
- Patients who have failed only one class of advanced therapy.
- "Pseudo-refractory" RA (persistent symptoms driven by non-inflammatory conditions, e.g., fibromyalgia, without objective evidence of active inflammation).
- Apparent treatment failure primarily driven by non-adherence.

Temporal Context

- **Target Patient State:** Prevalent. The focus is on patients with established disease and a documented longitudinal history of multiple treatment failures.

Clinical Granularity

- **Severity (Disease Activity):** High granularity required. Must demonstrate persistent moderate or high disease activity.
- **Acuity:** Chronic/Established disease state.
- **Etiology (Treatment History):** Very high granularity is mandatory. Identification requires documentation confirming failure of ≥2 b/tsDMARDs with different MOAs. Specific details regarding the sequence and outcomes of prior therapies, particularly JAK inhibitors, are essential.
- **Manifestation:** Requires evidence of both the specific treatment history AND current active disease.

Population Context

- Adults with a confirmed diagnosis of Rheumatoid Arthritis.

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4. Intended Clinical Application Research Utility

This phenotype is designed to support epidemiological research essential for the commercialization and market access strategies of novel therapeutic mechanisms and modalities (e.g., PD-1 agonists, Vagus Nerve Stimulation, FcRn inhibitors) entering the saturated RA market in the 2025-2026 horizon.

The primary utility is to characterize the D2T RA population, which represents the key opportunity for market differentiation where existing mechanisms (TNF inhibitors, IL-6 inhibitors, JAK inhibitors, T/B-cell modulators) have failed. This data is critical for:

1. **Quantifying Burden of Illness and HCRU:** Assessing the substantial clinical and economic burden and healthcare resource utilization associated with this multi-refractory population.
2. **Analyzing Real-World Treatment Patterns:** Characterizing the sequence, duration, and outcomes of advanced therapy cycling, with a specific focus on the unmet need in patients who have failed both biologics and JAK inhibitors.
3. **Market Access and HTA:** Generating evidence for Health Technology Assessments (HTA) and payer negotiations by demonstrating the significant inadequacy of the current standard of care.
4. **Comparative Effectiveness Research:** Designing studies to establish the value proposition of new mechanisms of action targeting this challenging patient segment.

Clinical Description: Rheumatoid Arthritis (RA) – Active, Persistent, Moderate-to-Severe

Synonyms: Severe, persistent RA

1. Clinical Case Definition

This phenotype defines established Rheumatoid Arthritis (RA) characterized by ongoing, active inflammation and persistent symptoms. It requires a prior confirmed diagnosis of RA (e.g., meeting ACR/EULAR classification criteria).

The clinical presentation includes persistent synovitis (objective joint swelling and tenderness), significant morning stiffness, fatigue, and polyarticular pain, frequently resulting in functional impairment and diminished quality of life.

The defining feature is objectively measured, persistent disease activity. This is confirmed by standardized composite measures (e.g., DAS28-CRP/ESR, CDAI, SDAI) consistently indicating moderate or high disease activity. Laboratory findings must support the presence of active systemic inflammation, typically evidenced by elevated acute phase reactants (C-reactive protein [CRP] and Erythrocyte Sedimentation Rate [ESR]). Imaging (ultrasound, MRI) is crucial for confirming the presence of active synovitis and distinguishing it from structural damage. Further evidence of this active state may include rapid radiographic progression or a persistent reliance on glucocorticoids due to underlying inflammation (e.g., inability to taper doses below 7.5mg prednisone equivalent/day). While common, seropositivity (Rheumatoid Factor [RF] or anti-citrullinated protein antibodies [ACPA]) is not required.

2. Phenotype Scope & Granularity

- **Temporal Context:** Prevalent. Focuses on patients with established disease and persistent, ongoing activity.
- **Severity:** Moderate or High disease activity only. This scope is not inclusive of mild RA or RA in remission/low disease activity.
- **Acuity / Chronicity:** Chronic, persistent disease state.
- **Etiology:** Autoimmune/Idiopathic (standard RA).
- **Population Context:** Adults.

3. Related Conditions & Scope Boundaries

The intent of this phenotype is to identify active inflammatory synovitis. Related conditions that may present with similar symptoms but lack objective evidence of inflammation (sometimes termed "pseudo-refractory" RA) are not within the scope of this phenotype.

- **Fibromyalgia and Central Pain Syndromes:** These non-inflammatory pain conditions are distinct from the inflammatory state defined here.
- **Secondary Osteoarthritis or Mechanical Joint Damage:** These represent structural issues and are distinct from active inflammatory synovitis.
- **Early or Treatment-Naïve Rheumatoid Arthritis:** These represent different phases of the disease trajectory and are not within the direct scope of this established, persistent phenotype.
- **Rheumatoid Arthritis in Remission:** Patients who have achieved remission are not within the scope of this active phenotype.

4. Key Complications & Common Comorbidities

The persistent inflammation characterizing this phenotype is associated with significant complications and comorbidities. These should be recognized as consequences or associations, not part of the core definition of the active RA state as they may represent a past active state which may currently be inactive.

- **Complications:** Irreversible joint damage, progressive disability.
- **Comorbidities:** Cardiovascular disease, serious infections (often exacerbated by chronic inflammation and/or immunosuppression), osteoporosis, interstitial lung disease.

5. Intended Data Sources

This clinical description is intended for building concept sets against real-world administrative claims, electronic health record (EHR) databases, and patient registries. The target data should be standardized to the OMOP Common Data Model. Examples of licensable data sources where this concept set would be applied include:

- **Optum®** (Clinformatics® Data Mart, SES, Pan-Therapeutic)
- **Merative™** (MarketScan® Commercial Claims and Encounters)
- **Veradigm** (Health Verity, Practice Fusion EHR)
- **IQVIA** (AmbEMR, PharMetrics Plus)
- **HealthVerity**