SPARKS

2026 MS TRIAL PLAYBOOK

1. Executive Summary - The Convergence

Where Biological Precision Meets Regulatory Rigor

The clinical development landscape for Multiple Sclerosis is undergoing its most significant transformation in nearly a decade. As we enter 2026, Sponsors and CROs face a unique "perfect storm": the operationalization of the **2024 Revised McDonald Criteria** coincides directly with the industry-wide adoption of **ICH-E6(R3)**.

While these two frameworks appear distinct (one clinical, one regulatory) their impact on your trials is inextricably linked. This Playbook outlines why they must be interpreted together to ensure trial success.

The Core Conflict: Diagnostic Shifts vs. Statistical Power

The 2024 McDonald Criteria represent a leap toward "biological diagnosis." By integrating the optic nerve as a fifth topographic location, accepting Kappa Free Light Chains (kFLC) as equivalent to OCBs, and enabling the diagnosis of MS in asymptomatic patients (formerly Radiologically Isolated Syndrome/RIS), we have fundamentally altered the "MS Patient" profile.

- **The Opportunity:** Access to a broader, earlier-stage patient pool.
- **The Risk:** "Endpoint Dilution." Patients diagnosed closer to the biological onset often display milder clinical disease activity. Protocols designed with 2017 assumptions regarding Annualized Relapse Rates (ARR) may fail to demonstrate efficacy in this new, "healthier" cohort. Recent data suggest that earlier diagnosis may lead to lower baseline Annualized Relapse Rates (ARR). Without recalibration, a study powered on 2017 historical data may be underpowered for a 2026 cohort.
- **Global Context:** It is important to note that adoption timelines for these criteria may vary between the FDA and EMA. Global protocols must build in regulatory flexibility to accommodate regional interpretations.

The Regulatory Solution: ICH-E6(R3) as a Strategic Tool

To mitigate the risks of this new patient phenotype, the ICH-E6(R3) guideline offers the necessary operational framework. R3 moves the industry beyond "checkbox compliance" toward **Quality by Design (QbD)** and **Data Governance**.

In this new era, complex diagnostic biomarkers, such as the Central Vein Sign (CVS) or Paramagnetic Rim Lesions (PRL), are not just eligibility criteria; they are **Critical to Quality (CtQ)** factors. Ensuring the integrity of this data requires a shift from 100% Source Data Verification (SDV) to **Risk-Based Quality Management (RBQM)**, utilizing centralized monitoring to detect diagnostic inconsistencies that on-site monitors might miss.

The Accelsiors Stance

We believe that compliance in 2026 is not merely about surviving an audit; it is about strategic recalibration. To succeed, clinical operations leaders must harmonize these two shifts. This means designing protocols that account for lower event rates while implementing data governance structures that ensure the reliability of advanced neuro-diagnostic tools.
This Playbook serves as your guide to navigating this convergence, ensuring your studies are not only compliant by design but statistically robust enough to prove efficacy in the modern era of MS.

2. The New Diagnostic Reality (McDonald 2024)

Operationalizing the Shift from "Clinical" to "Biological" Diagnosis

The 2024 Revised McDonald Criteria move the field toward a unified, biologically driven definition of MS. For clinical trial operations, this is not merely an academic update; it is a logistical reset. The expansion of diagnostic criteria offers a wider recruitment funnel, but it demands specific site capabilities and vendor setups to execute correctly.
Here are the four major shifts and their immediate operational implications for your protocols:

2.1. The Optic Nerve: A New "Site Capability" Gate

The Change: The optic nerve is now formally recognized as the fifth topographic location for demonstrating Dissemination in Space (DIS). A lesion here carries the same weight as a periventricular or spinal cord lesion.

Operational Implication:

- **Site Selection Mandate:** Sites that rely solely on clinical history for optic neuritis are now at a disadvantage. To compete for patients, your sites must have access to **Visual Evoked Potentials (VEPs)** or **Optical Coherence Tomography (OCT)**.
- **The Risk:** If your protocol does not explicitly accept VEP/OCT evidence for DIS, you will screen-fail patients that competitor trials (using the 2024 criteria) will enroll.
- **Action:** Audit your site list for neuro-ophthalmology capabilities immediately.

2.2. Kappa Free Light Chains (kFLC): The Efficiency Lever

The Change: The presence of kappa free light chains (kFLC index > 6.1) in CSF is now fully equivalent to Oligoclonal Bands (OCBs) for demonstrating Dissemination in Time (DIT).

Operational Implication:

- **Speed & Cost:** OCB analysis is labor-intensive, qualitative (visual interpretation), and slow. kFLC measurement is automated, quantitative (nephelometry/turbidimetry), and significantly faster.
- **Standardization:** Using kFLC removes the inter-rater variability associated with reading Western blots for OCBs.
- **Action:** Update your Central Lab manual and budget. Moving to kFLC can reduce screening turnaround times, but your central lab must be validated for the specific index threshold (> 6.1).

2.3 Specificity Tools (CVS & PRL): The Data Integrity "Firewall"

The Change: The criteria introduce "Rule-In" specificities using MRI biomarkers: the **Central Vein Sign (CVS)** and **Paramagnetic Rim Lesions (PRL)**. While not mandatory for every patient, they are strongly recommended for patients >50 years old or those with vascular comorbidities to avoid misdiagnosis.

Operational Implication:

- **Imaging Protocols:** Standard MRI sequences (T1/T2/FLAIR) are insufficient for detecting CVS or PRL. You must implement susceptibility-weighted imaging (SWI) or similar iron-sensitive sequences.
- **Reader Training:** Identifying a "rim lesion" requires specialized expertise. Local site radiologists may miss these or over-interpret artifacts.
- **Action:** These biomarkers must be treated as **Critical to Quality (CtQ)** factors under ICH-E6(R3). Their interpretation should be centralized to ensure that vascular mimics are not inadvertently enrolled in your MS trial.

2.4 The "Biological" Diagnosis (formerly RIS)

The Change: Individuals with "Radiologically Isolated Syndrome" (RIS), who have MRI lesions but no clinical symptoms, can now be diagnosed with MS if they meet specific paraclinical criteria.

Operational Implication:

- **Recruitment vs. Power:** This allows you to recruit patients at the earliest biological stage of the disease. However, these patients are often clinically "silent."
- **Endpoint Risk:** If your trial relies on Annualized Relapse Rates (ARR), enrolling these biologically early patients may dilute your event rate, potentially causing a study to fail on efficacy despite the drug working.
- **Action:** Protocols must stratify enrollment based on clinical history (symptomatic vs. biological diagnosis) to protect statistical power.

3. The Regulatory Safety Net (ICH-E6 R3)

Moving Beyond "Checkboxes" to Data Governance and Quality by Design

If the 2024 McDonald Criteria represent what we measure in modern MS trials, ICH-E6(R3) represents how we must protect the integrity of that measurement. The upcoming Revision 3 is not just an update to Good Clinical Practice (GCP); it is a fundamental shift from retrospective data checking to proactive **Data Governance** and **Quality by Design (QbD)**.

For MS trials involving complex neuro-diagnostics, the "one-size-fits-all" monitoring approach is now obsolete. Here is how to operationalize R3 to protect your study endpoints.

3.1 Defining "Critical to Quality" (CtQ) Factors in MS

The Change: R3 mandates that sponsors identify data points that are critical to the reliability of trial results and the safety of participants. These are your CtQ factors.

Operational Implication: You cannot monitor everything with equal intensity. You must identify where the "break points" are in your specific MS protocol.

- **Example:** In a trial recruiting early-stage patients based on the 2024 criteria, the **Optic Nerve Assessment (VEP/OCT)** and the **Kappa Free Light Chain (kFLC)** index are CtQ factors. If these are recorded incorrectly, the patient is not just a protocol deviation—they are a false enrollment.
- **Action:** In your initial Risk Assessment, formally designate specific biomarker acquisition and transfer processes as CtQ. This focuses your monitoring resources where they matter most.

3.2 From Source Data Verification (SDV) to Risk-Based Quality Management (RBQM)

The Change: R3 explicitly discourages 100% SDV (checking every number against the medical record) in favor of a risk-based approach.

Operational Implication:

- **Targeted Monitoring:** Instead of verifying every vital sign at every visit, your CRAs should focus on the "high-risk" data defined by your CtQ factors. For example, verifying that the MRI sequence used for a "Rule-In" diagnosis actually included susceptibility-weighted imaging (SWI) to detect Central Vein Signs.
- **Centralized Monitoring:** R3 places heavy emphasis on off-site review. Accelsiors utilizes centralized statistical monitoring to detect outliers, such as a site that reports 100% of their patients as having "typical" MRI presentations in an older population, which might suggest they are missing vascular comorbidities (a key specificity issue in the new criteria).
- **Action:** Rewrite your Monitoring Plan to reduce routine SDV by 30-40% and reallocate those hours to centralized data review and targeted eligibility verification.

3.3 Data Governance for Complex Biomarkers

The Change: R3 introduces the concept of "Data Governance"—ensuring data integrity throughout the data lifecycle, not just at the point of capture.

Operational Implication:

- **The Chain of Custody:** With kFLC replacing OCBs, the data is quantitative and automated. The risk is no longer "interpretation" (as with OCB bands) but "transfer." How does the number get from the nephelometer to the eCRF?
- **Imaging Data:** For MRI-based endpoints (CVS/PRL), the raw data files are massive and complex. Governance means ensuring the audit trail of the file transfer to the Central Reader is unbreakable.
- **Action:** Implement a Digital Data Management Plan that maps the flow of neuro-biomarker data. Ensure your vendors (labs/imaging centers) are audited specifically on their data transfer security, not just their analytical capabilities.

3.4 Establishing Quality Tolerance Limits (QTLs)

The Change: You must establish predefined limits for trial quality parameters. If these limits are breached, a root cause analysis is triggered.

Operational Implication:

- **Diagnostic Drift:** Establish a QTL for "Screen Failures due to Misdiagnosis." If a site has a screen fail rate significantly *lower* than the global average in an era of complex criteria, they may be over-diagnosing patients.
- **Action:** Set a QTL for diagnostic verification. For example: *"If >5% of enrolled patients are flagged by Medical Monitoring as having 'indeterminate' MRI findings, trigger an immediate site audit."*

3.5: Enhancing Patient Centricity via ICH-E6(R3)

Designing for the "Early" Patient

While the 2024 McDonald Criteria allow us to recruit patients earlier in their disease course, this creates a unique operational paradox: **The "Healthy Patient" Challenge.**

Patients diagnosed at the biological onset (formerly RIS) or early clinical stages often have minimal disability (EDSS 0–1.5). Unlike late-stage progressive populations, these participants are likely fully employed, active, and less tolerant of the high burden associated with traditional site-centric protocols.

ICH-E6(R3) as the Enabler for Decentralization

The new R3 guideline explicitly supports "fit-for-purpose" data collection methods, validating the use of decentralized clinical trial (DCT) elements provided the data governance is sound. To improve retention in this new "milder" cohort, we recommend the following:

- **The Diagnostic Experience:** Moving from mandatory OCBs (Western Blot) to automated **Kappa Free Light Chains (kFLC)** is not just a lab efficiency; it is a patient benefit. The speed and definitive nature of kFLC reduce the anxiety of "indeterminate" results and the potential need for repeat lumbar punctures.
- **Hybrid Monitoring:** Leverage R3's support for off-site data collection. For safety labs or routine vitals, utilize home health nursing or local labs rather than requiring travel to the primary investigative site.
- **eCOA/ePRO Strategy:** "Silent" progression (PIRA) is a key endpoint for early-stage patients. Utilizing high-frequency digital biomarkers (e.g., active tests via smartphone apps or wearables) provides more granular data on disability accumulation than infrequent in-clinic EDSS assessments, while respecting the patient's time.

Pro Tip: Not sure if your ePRO strategy meets R3 governance standards? Accelsiors offers a specific 'Patient Burden Assessment' as part of our protocol audit.

4. Operational Strategic Pillars

Turning Regulatory Complexity into Competitive Advantage

Knowing the new criteria is one thing; executing a trial that leverages them without drowning in operational noise is another. This is where the "Secret Sauce" comes in. At Accelsiors, we believe the convergence of McDonald 2024 and ICH-E6(R3) requires a fundamental recalibration of how MS trials are designed and monitored.

Here are four strategic pivots that move your trial from "compliant" to "high-performance."

4. 1 Recalibrating Endpoints: The "Dilution" Defense

The Risk: By including "Biological MS" (formerly RIS) and early-stage patients via Optic Nerve diagnosis, you are recruiting a healthier population. If your primary endpoint relies solely on Annualized Relapse Rate (ARR), your study is at high risk of failure due to low event rates.

The Strategy: Shift the focus from "Noise" (Relapses) to "Silence" (Progression).

- **PIRA Integration:** We recommend incorporating **Progression Independent of Relapse Activity (PIRA)** as a key secondary or composite endpoint.
- **NEDA-3 vs. NEDA-4:** Move to NEDA-4 (No Evidence of Disease Activity), which includes brain volume loss. This captures the "silent" disease activity present in early-stage patients that ARR misses.
- **The Operational Fix:** Train sites that "stability" is not always "efficacy." Monitors must be trained to look for subtle signs of disability worsening (CDW) even in the absence of acute relapses.

4.2 Site Feasibility 2.0: The "Optic Nerve" Audit

The Risk: Many "experienced" MS sites lack the specific neuro-ophthalmology infrastructure required by the 2024 criteria.

The Strategy: Don't ask generic questions.

- **The VEP/OCT Mandate:** During feasibility, we do not ask "Do you have access to ophthalmology?" We ask: *"Can you perform Visual Evoked Potentials (VEP) or OCT with a 48-hour turnaround for screening eligibility?"*
- **The Result:** We filter out sites that will become bottlenecks. If a site cannot assess the optic nerve quickly, they cannot recruit the 15-20% of patients who qualify via this new topographic criterion.

4.3 Leveraging kFLC for Velocity

The Risk: Lumbar punctures are a barrier, and Oligoclonal Band (OCB) analysis is slow (Western Blot) and subjective.

The Strategy: Standardize on Kappa Free Light Chains (kFLC).

- **The Efficiency:** kFLC analysis is automated (nephelometry), quantitative, and significantly faster than OCBs.
- **The Operational Fix:** We write the Central Lab Protocol to prioritize kFLC Index (>6.1) as the primary DIT (Dissemination in Time) evidence.
- **The Win:** This reduces the screening window by days and eliminates "indeterminate" OCB results that lead to unnecessary screen failures.

4.4 Centralized "Gatekeeper" Monitoring (R3 Compliance)

The Risk: The new specificity markers, Central Vein Sign (CVS) and Paramagnetic Rim Lesions (PRL), are difficult to read. Relying on local radiologists will lead to data variability and potential "vascular mimics" entering the trial.

The Strategy: Implement a Centralized Imaging Gatekeeper.

- **R3 Alignment:** This fulfills the ICH-E6(R3) requirement for "Data Governance" of complex data streams.
- **The Process:** Raw MRI data (specifically SWI sequences) is uploaded immediately to a central platform. AI-assisted or expert central review confirms the presence of CVS/PRL *before* randomization.
- **The Win:** You ensure a "pure" MS population, protecting your signal-to-noise ratio and satisfying regulatory auditors that you have controlled the risk of misdiagnosis.

Case Study (Hypothetical) brings everything together. It demonstrates how the **Diagnostic Precision** (McDonald 2024) and **Regulatory Rigor** (ICH-E6 R3) work in practice to save a study.

5. Case Study

Note: This case study is a composite based on recent operational pivots. Individual study results will vary based on therapeutic indication and site mix.

The "Protocol Pivot": Rescuing a Phase II Trial with 2025 Standards

Theory is useful, but execution is what delivers data. To illustrate the impact of the "Convergence" between McDonald 2024 and ICH-E6(R3), let's look at a hypothetical rescue scenario based on the current transition period.

The Scenario

The Study: A Phase IIb study in Relapsing Multiple Sclerosis (RMS).
The Status: 14 months into recruitment, the study is trending 30% behind schedule.
The Bottleneck: High screen failure rates. Sites are rejecting early-stage patients due to "insufficient evidence of Dissemination in Time (DIT)" under 2017 criteria (waiting for a second clinical attack) or indeterminate Oligoclonal Band (OCB) results.

The Accelsiors Intervention

We proposed a "Protocol Pivot" to align the study with the 2024 Revised McDonald Criteria while simultaneously implementing an ICH-E6(R3) Data Governance layer to protect endpoint integrity.

Step 1: The Diagnostic Expansion (Widening the Funnel)

- **Optic Nerve Inclusion:** We amended the protocol to accept the Optic Nerve as a qualifying lesion location.
- *Result:* Patients presenting with isolated optic neuritis—previously requiring a long wait for a second attack or spinal MRI, became eligible immediately via VEP/OCT confirmation.
- **Switch to kFLC:** We replaced the mandatory Western Blot for OCBs with the **Kappa Free Light Chain (kFLC) index.**
- *Result:* Lab turnaround time dropped from 10 days to 48 hours. Borderline OCB cases became definitive "Positives" (Index > 6.1), salvaging 12% of previous screen failures.

Step 2: The Regulatory Safety Net (Protecting the Data)

With the funnel widened to include earlier, "milder" patients, the Sponsor feared diagnostic dilution (enrolling patients who don't actually have MS).

- **CtQ Identification:** We designated "Diagnostic Specificity" as a Critical to Quality (CtQ) factor.
- **Centralized Gatekeeper:** We implemented a centralized imaging review focusing on the **Central Vein Sign (CVS)** for any patient over age 50 or with vascular risk factors.
- *Result:* We identified and excluded 4 patients who met the *clinical* criteria but lacked the specific MRI biomarkers, preventing costly "non-responder" noise in the final data.

The Outcome

By harmonizing the 2024 Criteria with R3 rigor, the study trajectory changed within 4 months:

- **Recruitment Rate:** Increased by **18%** (driven by Optic Nerve and kFLC efficiency).
- **Screen Failure Rate:** Decreased by **22%.**
- **Data Integrity:** Zero audit findings related to eligibility during the interim analysis, thanks to the documented R3 Data Governance plan.

Conclusion: Future-Proofing Your MS Pipeline

The release of the 2024 McDonald Criteria is the biggest shift in MS clinical trials in a generation. Simultaneously, ICH-E6(R3) is changing the rules of engagement for how those trials are monitored.

You can view these as two separate burdens, or you can view them as a singular opportunity to run faster, more precise, and more compliant trials.

- **McDonald 2024** gives you the speed (earlier diagnosis).
- **ICH-E6(R3)** gives you the safety (risk-based quality).

At **Accelsiors**, we don't just read the guidelines; we operationalize them. Whether you are designing a new protocol for 2026 or need to recalibrate an ongoing study, our team is ready to help you navigate the convergence.

Partner with Accelsiors to co-create your patient-centric future.

Visit www.accelsiors.com

Schedule a 30-Minute Consultation with our Medical Team
bdglobal@accelsiors.com | +41 41 799 69 40 | LinkedIn

From Strategy to Execution: Assessing Your Protocol

Understanding the convergence of McDonald 2024 and ICH-E6(R3) is the first step; applying it to your study design is the second. To help you determine if your current or upcoming protocol is ready for this new landscape, we have developed the **10-Point Protocol Audit Checklist**.

This tool distills the complex diagnostic shifts (like the Optic Nerve and kFLC inclusion) and regulatory requirements (CtQ factors) discussed above into actionable criteria. Use this to 'stress-test' your protocol before your next regulatory submission or site initiation. Use this tool to grade your current or upcoming protocols. (High/Med Priority indicates risk level if unchecked).

Category A: Diagnostic Precision (McDonald 2024 Alignment)

☐ **The "Optic Nerve" Check:** Does the protocol explicitly list Optic Nerve involvement (validated by VEP or OCT) as a qualifying DIS criterion? *(If no, you are restricting your recruitment pool.)*

Priority: **High**
Notes: _____

☐ **The kFLC Efficiency:** Does the protocol accept Kappa Free Light Chains (kFLC index > 6.1) as an alternative to OCBs? *(If no, you are adding unnecessary cost and time.)*

Priority: **Med**
Notes: _____

☐ **Specificity Guardrails:** For patients >50 years old or with vascular risk factors, does the protocol mandate "Rule-In" features like CVS, PRL, or spinal cord lesions? *(Rationale: Reduces risk of enrolling vascular mimics.)*

Priority: **High**
Notes: _____

☐ **The Symptomatic Gate:** Does the inclusion criteria account for "Biological MS" (formerly RIS) transitioning to MS? *(Rationale: Captures early-stage population.)*

Priority: **Med**
Notes: _____

Category B: Regulatory Rigor (ICH-E6 R3 Compliance)

- [ ] **Critical to Quality (CtQ) Identification:** Have specific data points (e.g., MRI sequence quality, kFLC transfer) been formally identified as CtQ factors in the monitoring plan?

  Priority: **High**
  Notes: _____

- [ ] **Data Governance Plan:** Does your Data Management Plan explicitly map the transfer of raw OCT/MRI data from site to central reader to meet R3 governance standards?

  Priority: **High**
  Notes: _____

- [ ] **Targeted Monitoring:** Has the monitoring plan moved away from 100% SDV to a risk-based approach focusing on eligibility and safety outliers?
  Priority: **Med**
  Notes: _____

- [ ] **Quality Tolerance Limits (QTLs):** Have you established QTLs for diagnostic accuracy? (e.g., "If >5% of randomized patients are misdiagnosed, trigger RCA.")

  Priority: **High**
  Notes: _____

Category C: Strategic Design

- [ ] **Endpoint Sensitivity:** Have sample size calculations been stress-tested against lower-than-historical annualized relapse rates due to milder patient phenotypes?

  Priority: **High**
  Notes: _____

- [ ] **Patient Centricity:** Does the protocol utilize decentralized elements (e.g., home health, ePRO) to reduce burden on early-stage, active patients?

  Priority: **Med**
  Notes: _____

Did you check *'No'* on more than three items?
Your protocol may be at risk of significant recruitment delays or regulatory queries.

>> Schedule a review with our Medical Team