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Perspective

Should Randomized Clinical Trials Remain the Primary Evidence for Evaluating New Therapeutic Regimens in Leprosy? Introducing Deep Phenotyping Real-World Evidence (DP-RWE) as a Methodological Framework

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Abstract

Leprosy remains a major cause of peripheral neuropathy and permanent disability, with current multidrug regimens challenged by toxicity, treatment duration, and relapse. Although therapeutic innovation is an urgent priority, conventional Phase III randomized controlled trials (RCTs) face substantial economic, logistical, and ethical constraints in neglected diseases, while routine Real-World Evidence (RWE) lacks granular biological resolution. To bridge this gap, this Perspective introduces Deep Phenotyping Real-World Evidence (DP-RWE), a standardized clinical research framework integrating Deep Phenotyping and RWE into a prospective, longitudinal architecture for therapeutic evaluation under routine clinical conditions. Built upon four core principles: Standardization, Deep Phenotyping (DP), Longitudinal Assessment, and Real-World Applicability, the framework organizes prospective clinical, microbiological, histopathological, molecular, immunological, neurophysiological, and imaging domains tailored to specific therapeutic questions. Grounded in over two decades of reference-center cohort research, DP-RWE demonstrates that longitudinally integrating multimodal biomarkers captures distinct biological dimensions of therapeutic response, therapeutic failure, and relapse under real-world practice. Ultimately, DP-RWE does not replace RCTs but complements them, establishing a reproducible, biologically informative pathway to evaluate innovative therapeutic regimens and advance precision medicine in endemic regions.

Keywords: leprosy; *Mycobacterium leprae*; deep phenotyping; real-world evidence; therapeutic evaluation; treatment outcomes; neglected tropical diseases

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Academic Editor:
Antonella d'Arminio Monforte

Received: 17 September 2026
Revised: 22 October 2026
Accepted: 26 October 2026
Published: 28 October 2026

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1. Introduction

More than four decades after the introduction of multidrug therapy (MDT), leprosy treatment has been profoundly transformed, yet therapeutic innovation remains an important scientific and clinical need. World Health Organization (WHO)-recommended MDT remains the cornerstone of leprosy treatment; however, relevant therapeutic challenges persist, including drug-related adverse effects, antimicrobial resistance, therapeutic failure in

selected patients, and relapse after treatment [1–7]. Importantly, these outcomes represent related but distinct clinical and biological phenomena and cannot necessarily be adequately characterized by clinical assessment or by a single therapeutic endpoint.

This complexity is particularly relevant because therapeutic response in leprosy extends beyond antimicrobial activity alone. Studies addressing antimicrobial resistance, treatment failure, bacillary persistence or viability, adverse drug reactions, neurological outcomes, and post-treatment relapse illustrate that different clinical and biological measures may capture complementary dimensions of treatment performance [2–7]. Accordingly, the evaluation of innovative therapeutic regimens requires methodologies capable of characterizing effectiveness, safety, bacteriological and biological response, neural outcomes, reactional episodes, disability, therapeutic failure, and long-term relapse, with the relevant dimensions selected according to the therapeutic question.

RCTs remain the preferred design for establishing therapeutic efficacy and safety whenever feasible and appropriate. Nevertheless, therapeutic questions in leprosy may extend beyond efficacy under controlled conditions to include effectiveness in heterogeneous clinical populations, adverse drug events during routine care, biological and neurological trajectories during and after treatment, therapeutic failure, and late relapse. These questions may require prolonged longitudinal observation and must be investigated within the broader context of neglected tropical diseases (NTDs), for which research investment remains disproportionately limited relative to disease burden, and drug repurposing represents an important strategy for therapeutic development [8]. These considerations do not diminish the value of RCTs; rather, they highlight the need for complementary approaches capable of generating rigorous longitudinal therapeutic evidence under real-world clinical conditions.

RWE provides an established approach for generating evidence on the use and potential benefits or risks of medical interventions from the analysis of Real-World Data (RWD), which include data relating to patient health status and/or healthcare delivery routinely collected from a variety of sources [9]. RWE should therefore not be equated solely with administrative claims or conventional electronic health records. Nevertheless, depending on the research question and data source, routinely collected information may lack the disease-specific microbiological, histopathological, molecular, neurological, imaging, and other biological resolution required for multidimensional therapeutic evaluation in leprosy. DP, in turn, has been defined as the precise and comprehensive analysis of phenotypic abnormalities [10]. The potential value of integrating DP with RWE therefore lies not in either concept individually, but in embedding high-resolution, disease-specific phenotypic characterization within prospectively planned longitudinal investigation conducted under real-world clinical conditions.

Importantly, the individual methodological components required for such an approach are not new. In leprosy, the International Federation of Anti-Leprosy Associations (ILEP) Nerve Function Impairment and Reactions (INFIR) Cohort Study demonstrated the feasibility of prospective, standardized, longitudinal, multidimensional assessment by combining detailed clinical and neurological evaluation with neurophysiological and quantitative sensory and motor measurements and biological specimen collection [11,12]. Comparable methodological precedents exist in other diseases. In tuberculosis, RePORT International established prospective observational cohorts linked through common protocols for clinical data and biological specimen collection, while RePORT-Brazil demonstrated an approach for evaluating the representativeness of a multicenter observational cohort against national surveillance data [13,14]. In psoriasis, the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) established large-scale prospective real-world therapeutic follow-up, while Psoriasis Stratification to Optimise Relevant Therapy (PSORT)

incorporated longitudinal clinical response with high-dimensional molecular phenotyping across tissues and time points [15,16].

These precedents clarify both what is already established and what remains to be structured. Prospective cohorts, longitudinal follow-up, standardized data collection, biological sampling, multidimensional phenotyping, and RWE are not individually novel methodological concepts. The methodological gap addressed in this Perspective is more specific: the lack of an explicitly articulated, disease-specific framework organized around the prospective, longitudinal, multidimensional evaluation of antimicrobial therapeutic regimens in leprosy under real-world clinical conditions. To address this gap, we introduce DP-RWE as a prospective, longitudinal, modular, disease-specific, and treatment-centred methodological framework for therapeutic evaluation in leprosy. DP-RWE is not proposed as a new epidemiological study design and is not intended to replace RCTs. Rather, it provides a structured approach through which clinical, microbiological, histopathological, molecular, immunological, neurological, imaging, and therapeutic outcome domains can be selected according to the therapeutic question, prospectively standardized, and longitudinally integrated under real-world clinical conditions (Figure 1).

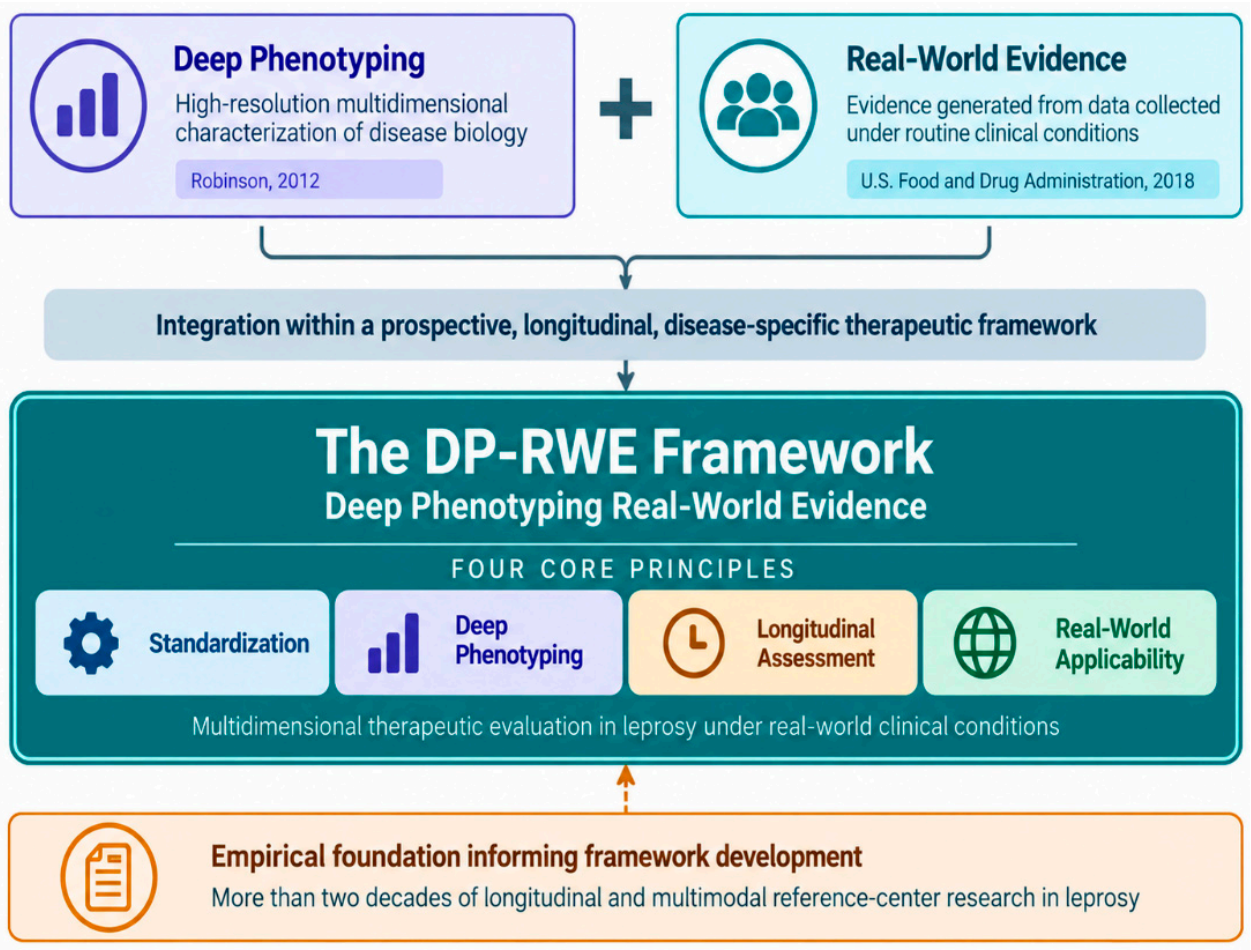


Figure 1. Conceptual foundation of the Deep Phenotyping Real-World Evidence (DP-RWE) framework. DP-RWE integrates established principles of Deep Phenotyping and Real-World Evidence within a prospective, longitudinal, modular, disease-specific, and treatment-centered framework for multidimensional therapeutic evaluation in leprosy under real-world clinical conditions [9,10]. More than two decades of longitudinal and multimodal reference-center research in leprosy provided empirical experience that informed the conceptual development of the framework but does not constitute a prerequisite for its application.

DP-RWE is built upon four core principles: standardization, DP, longitudinal assessment, and real-world applicability. Its modular structure does not require every study to employ all phenotyping domains, identical technologies, or uniform assessment schedules. Instead, the relevant domains, methods, assessment schedules, outcomes, and analytical strategies should be prespecified according to the therapeutic question, scientific objectives, and study design. This Perspective first examines the methodological gap that motivates the framework, then defines its conceptual basis, core principles, and operational domains, and finally discusses the methodological and empirical foundations that informed its development.

2. The Methodological Gap

Therapeutic evaluation in leprosy presents a distinctive methodological challenge because treatment response encompasses multiple clinical and biological processes that may evolve at different rates and over different time scales. Clinical improvement, bacteriological response, bacillary viability, histopathological activity, molecular detection of *Mycobacterium leprae*, neurological impairment, reactional episodes, adverse drug events, therapeutic failure, and relapse represent complementary but not necessarily synchronous dimensions of treatment response. Consequently, the apparent success or failure of a therapeutic regimen may depend substantially on which outcomes are assessed, how they are defined, and when they are measured [2–7].

Antimicrobial resistance illustrates only one component of this complexity. In a former leprosy colony in the Brazilian Amazon, Rosa et al. identified drug- and multidrug-resistant *M. leprae* among relapsed and newly diagnosed patients and provided molecular epidemiological evidence consistent with intrafamilial transmission of resistant strains [2]. This exceptional epidemiological setting should not be extrapolated to Brazil as a whole. In the Brazilian National Surveillance Plan, resistance-associated polymorphisms were identified in 16 of 1183 patients investigated (1.4%), including cases evaluated because of relapse or suspected treatment failure, and multidrug resistance involving dapsone and rifampicin was documented [3]. These findings establish antimicrobial resistance as a clinically relevant therapeutic outcome while also showing why resistance cannot, by itself, account for the broader spectrum of unfavorable post-treatment outcomes.

Therapeutic failure further demonstrates the need to distinguish related but non-equivalent biological phenomena. In a case–control study of 80 patients, Dornelas et al. compared 40 treatment-failure cases with 40 controls and integrated clinical information with histopathological, histological bacillary index, anti-PGL-I serological, and molecular parameters. Persistent histopathological abnormalities and bacillary burden after MDT were associated with subsequent treatment failure, illustrating the potential value of complementary biological measurements beyond clinical assessment alone [5]. More recently, Fonseca et al. evaluated multibacillary patients after completion of an extended 24-dose MDT regimen using complementary histopathological, bacteriological, molecular, neurological, sequencing, and nude-mouse footpad approaches. Different methods detected evidence of persistent bacillary activity or viability, whereas known resistance-associated mutations were uncommon [6]. Thus, therapeutic failure, persistent biological activity, bacillary viability, and antimicrobial resistance should not be treated as interchangeable outcomes.

Therapeutic performance also encompasses safety and long-term outcomes. In a retrospective cohort of 433 patients treated under routine clinical conditions, Celestino et al. compared adverse drug reactions associated with WHO-MDT and the rifampicin–ofloxacin–minocycline (ROM) regimen, incorporating clinical and laboratory variables together with temporality, severity, and causality assessment [4]. At the other end of the therapeutic timeline, relapse may become evident years after treatment completion. A recent systematic review including 26 studies and 71,385 participants demonstrated

substantial heterogeneity in reported relapse across geographic settings and treatment regimens, reinforcing the importance of prolonged post-treatment observation and careful interpretation of relapse as a therapeutic outcome [7].

These observations have direct methodological implications for therapeutic research. RCTs remain fundamental for estimating treatment efficacy and safety under prespecified experimental conditions, but not every clinically relevant question in leprosy is confined to comparative efficacy during the active treatment period. Evaluation of therapeutic effectiveness in heterogeneous populations, adverse drug events under routine care, biological response trajectories, neurological outcomes, treatment failure, and late relapse may require complementary longitudinal evidence extending beyond conventional trial endpoints. In NTDs, these challenges occur in a broader research environment characterized by disproportionately limited investment and substantial reliance on repurposed drugs for therapeutic development [8]. The issue is therefore not whether RCTs should be replaced, but which therapeutic questions require complementary forms of evidence and how such evidence can be generated rigorously.

RWE provides an important opportunity in this context because therapeutic performance can be investigated under routine clinical conditions and across patient populations that may differ from those enrolled in controlled trials [9]. However, the methodological value of RWE depends on the research question and on the quality, completeness, granularity, temporal structure, and clinical relevance of the underlying data. Routinely collected health information may be entirely appropriate for some questions but insufficient for therapeutic questions requiring disease-specific microbiological, histopathological, molecular, immunological, neurological, or imaging measurements. Conversely, the prospective collection of numerous high-resolution variables does not, by itself, eliminate selection bias, confounding by indication, missing data, measurement error, or other limitations inherent to observational research. Appropriate design and analytical strategies must therefore be prespecified according to the question being investigated.

The methodological challenge is consequently neither to replace RCTs with RWE nor simply to increase the number of measurements collected. Rather, it is to determine which dimensions of therapeutic response are relevant to a prespecified therapeutic question, how they should be measured, when they should be assessed, and how discordant or complementary findings across domains should be longitudinally integrated. This is particularly important in leprosy because clinical, bacteriological, molecular, histopathological, neurological, safety, and long-term outcomes may reflect different components of therapeutic response and may not evolve synchronously. Without an explicit structure linking the therapeutic question to the selection, timing, standardization, and longitudinal integration of these domains, multidimensional data may remain a collection of parallel measurements rather than an integrated evaluation of treatment performance.

Methodological precedents demonstrate that important components of such an approach are already feasible. In leprosy, the INFIR Cohort Study prospectively followed 303 newly diagnosed multibacillary patients for two years using standardized clinical and neurological examinations together with nerve conduction studies, quantitative sensory testing, vibrometry, dynamometry, monofilament testing, voluntary muscle testing, and biological specimen collection [11]. Subsequent analyses demonstrated the value of complementary methods for identifying early neurological abnormalities beyond conventional clinical nerve-function assessment [12]. INFIR therefore provides an important disease-specific precedent for prospective, standardized, multidimensional longitudinal phenotyping, although its principal purpose was the investigation of neuropathy and reactions rather than the evaluation of antimicrobial therapeutic regimens.

Relevant precedents are also available outside leprosy. RePORT International established a collaborative tuberculosis research platform based on prospective observational cohorts, harmonized clinical information, standardized specimen collection, and biorepositories, while RePORT-Brazil subsequently demonstrated an approach for examining the representativeness of a multicenter prospective cohort against national surveillance data [13,14]. In psoriasis, BADBIR established a large prospective observational infrastructure for longitudinal assessment of treatment exposure, safety, disease activity, and effectiveness, whereas PSORT incorporated high-dimensional molecular phenotyping into the investigation of treatment response, including longitudinal transcriptomic and proteomic measurements across blood and skin tissues [15,16]. These initiatives differ substantially in disease, purpose, scale, and methodology, but collectively demonstrate that prospective real-world follow-up, standardized data collection, biological sampling, and high-resolution phenotyping can be integrated within longitudinal research infrastructures.

Taken together, these precedents demonstrate that the individual methodological components required for high-resolution longitudinal therapeutic research are already available. The gap is not the absence of prospective cohorts, longitudinal follow-up, real-world observational research, biological sampling, or multidimensional phenotyping in leprosy. Rather, these methodological components remain dispersed across studies designed to address specific dimensions of disease or treatment response, without an explicitly articulated, disease-specific framework that prospectively selects, standardizes, and longitudinally integrates relevant phenotyping domains around the multidimensional evaluation of antimicrobial therapeutic regimens under real-world clinical conditions. DP-RWE is proposed to address this integrative methodological gap while remaining modular enough to accommodate different therapeutic questions, regimens, populations, technologies, and outcome domains. The following section defines the framework, its four core principles, and its operational domains.

Modularity is a design principle rather than a hierarchy of available tests. For each prespecified therapeutic question, investigators should identify the domains necessary to characterize the expected treatment effects and safety outcomes and justify which complementary measures can be reliably collected. No universal combination of examinations is required; omission of a measure essential to the research question must be acknowledged as a design limitation rather than treated as an equivalent lower-resource phenotype.

3. Results

To address the methodological gap identified above, we introduce DP-RWE as a prospective, longitudinal, modular, disease-specific, and treatment-centred methodological framework for multidimensional therapeutic evaluation in leprosy under real-world clinical conditions. The framework brings together the established concepts of DP, defined as the precise and comprehensive characterization of phenotypic abnormalities [10], and RWE, generated from the analysis of data relating to patient health status and/or healthcare delivery routinely collected from a variety of sources [9]. Rather than proposing a new epidemiological study design, diagnostic tool, or single data-collection technique, DP-RWE provides a structured methodology for organizing and integrating complementary clinical and biological information around a prespecified therapeutic question. Its purpose is to support multidimensional evaluation of therapeutic effectiveness, safety, biological response, neurological outcomes, treatment failure, and long-term relapse under real-world clinical conditions [4–7].

DP-RWE is structured around four interdependent core principles: standardization, DP, longitudinal assessment, and real-world applicability. Together, these principles define how therapeutic questions are translated into a prospectively planned and method-

ologically coherent evaluation. Standardization refers to the prospective definition of the research question, relevant data and phenotyping domains, assessment procedures, outcomes, follow-up, and analytical approach, consistent with established recommendations concerning data fitness, study design, prespecified protocols, and analytical planning in the generation of RWE [9,17]. DP provides precise and comprehensive multidimensional characterization through complementary clinical and biological domains selected according to the therapeutic question [10]. Longitudinal assessment enables therapeutic response and relevant outcomes to be evaluated over time, recognizing that different clinical and biological dimensions may follow distinct temporal trajectories, as illustrated by prospective multidimensional cohort studies in leprosy and other chronic infectious diseases [11,13]. Real-world applicability situates this structured evaluation within routine clinical conditions, allowing therapeutic performance to be investigated in the populations and circumstances in which treatment is delivered [9].

The operational structure of DP-RWE is modular rather than prescriptive: not every therapeutic study is expected to include all phenotyping domains, technologies, or assessment schedules. Instead, the components of the framework should be selected according to the therapeutic question, characteristics of the regimen and study population, biological plausibility, expected treatment effects, relevant safety concerns, and technical feasibility. Within this structure, eight complementary operational domains may be considered: clinical phenotyping, microbiology, histopathology, molecular biology, immunology, neurology and electrophysiology, imaging, and therapeutic outcomes. The value of combining different domains is supported by leprosy studies showing that clinical assessment, bacillary burden, histopathological activity, molecular detection, serological markers, antimicrobial resistance, neurological evaluation, and long-term outcomes may provide complementary and sometimes non-equivalent information about disease status and therapeutic response [2,3,5–7]. Accordingly, the methodological strength of DP-RWE derives not from maximizing the number of measurements performed, but from selecting and longitudinally integrating the domains that are scientifically relevant to the prespecified therapeutic question.

The eight operational domains are intended to capture distinct but complementary dimensions of therapeutic response. Clinical Phenotyping characterizes the evolution of cutaneous manifestations, peripheral nerve involvement, reactional episodes, disability, and other clinically relevant outcomes; microbiology addresses bacillary burden and antimicrobial susceptibility; histopathology evaluates tissue-level evidence of inflammatory and bacillary activity; and molecular biology can provide sensitive detection and quantification of *M. leprae* DNA and, when specifically investigated, molecular markers associated with antimicrobial resistance [2,3,5,6]. Immunology may provide complementary characterization of host response and immunological events during and after treatment, including serological markers associated with the subsequent occurrence of leprosy reactions [18], whereas neurology and electrophysiology characterize peripheral nerve impairment and its evolution through clinical and neurophysiological measurements, allowing objective identification and characterization of distinct patterns of neural dysfunction across the leprosy spectrum [11,12,19,20]. Imaging, particularly high-resolution peripheral nerve ultrasonography, can provide objective structural characterization of nerve involvement, including nerve enlargement and asymmetry, when relevant to the therapeutic question [21,22], while therapeutic outcomes integrate treatment effectiveness, safety, adverse drug reactions, therapeutic failure, and post-treatment relapse according to prespecified definitions and follow-up periods [4,5,7]. These domains are therefore not independent endpoints to be accumulated indiscriminately, but complementary sources of information whose selection and longitudinal integration should be determined by the biological and clinical dimensions of the therapeutic question under investigation.

A defining feature of DP-RWE is that the selected operational domains are not assessed as isolated components but are prospectively integrated across clinically and biologically relevant time points. The timing and frequency of assessments should therefore be prespecified according to the therapeutic regimen, expected biological dynamics, safety profile, and outcomes of interest rather than imposed as a fixed schedule across all studies. Longitudinal studies in leprosy have demonstrated that clinical, neurological, histopathological, bacteriological, serological, and molecular findings may evolve differently during and after treatment, supporting the need to interpret therapeutic response across complementary domains and over time [5–7,18]. Within DP-RWE, baseline characterization establishes the reference phenotype against which subsequent changes can be interpreted, while repeated assessments during treatment and post-treatment follow-up allow the trajectories of selected domains to be examined in relation to therapeutic exposure and relevant outcomes. This operational sequence from a prespecified therapeutic question, through baseline characterization, selection and longitudinal assessment of relevant phenotyping domains, to multidimensional therapeutic outcomes constitutes the workflow of the DP-RWE framework (Figure 2).

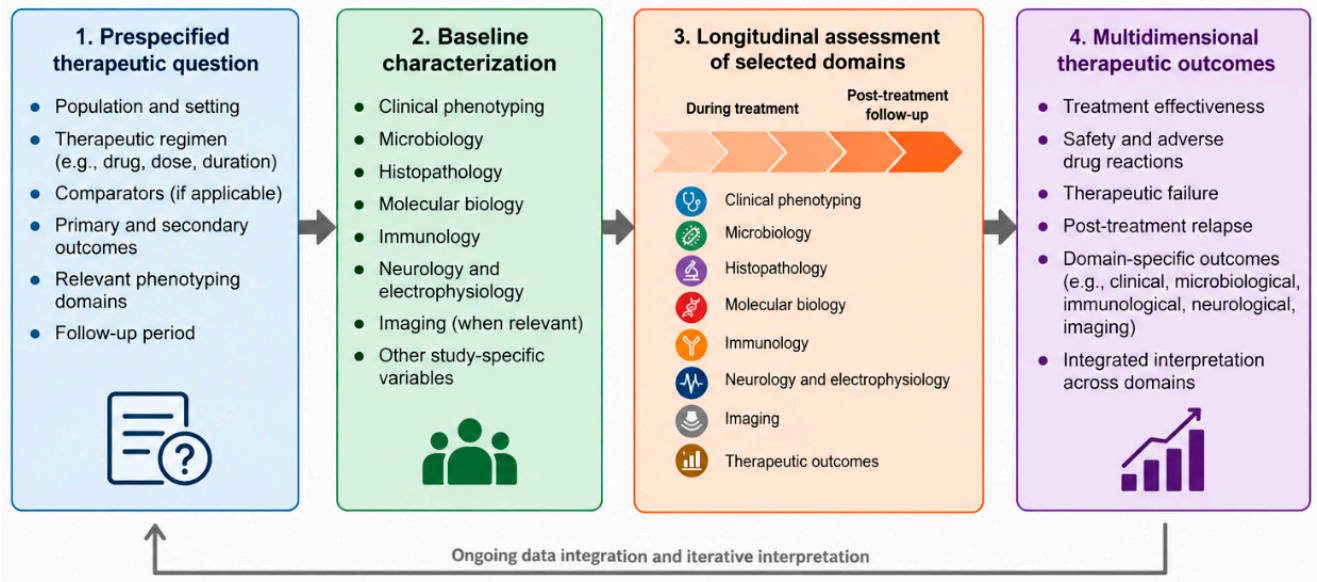


Figure 2. Operational workflow of the Deep Phenotyping Real-World Evidence (DP-RWE) framework. The workflow begins with a prespecified therapeutic question, followed by baseline characterization and the selection of relevant phenotyping domains for prospective longitudinal assessment during treatment and post-treatment follow-up. Multidimensional therapeutic outcomes are interpreted through ongoing integration of information across the selected domains. The operational domains are modular and should be selected according to the therapeutic question, regimen, study population, biological relevance, and technical feasibility; therefore, not all domains are required in every DP-RWE study.

For example, in an investigation of suspected treatment failure in multibacillary leprosy, a prespecified therapeutic question may require longitudinal clinical and neurological examinations together with bacteriological, histopathological, quantitative molecular and immunological measures, selected according to biological relevance. Discordant findings should trigger contextual interpretation and further investigation, not automatic classification as failure. Molecular detection of *M. leprae* DNA alone does not establish bacillary viability or treatment failure.

This operational workflow provides a flexible structure for prospective therapeutic evaluation without imposing a uniform set of tests, technologies, or assessment schedules

across studies. The specific combination of phenotyping domains should be determined by the therapeutic question, characteristics of the regimen and study population, biological relevance, outcomes of interest, and technical feasibility, while preserving the four core principles of the framework. The definition, core principles, operational domains, and guiding principle of DP-RWE are summarized in Table 1.

Table 1. Definition and Operational Components of the Deep Phenotyping Real-World Evidence (DP-RWE) Framework.

Component	Definition	Methodological Function
Definition	Prospective, longitudinal, modular, treatment-centered integration of deep phenotyping and real-world evidence.	Specify the therapeutic question and the scope of the framework.
Core principles	Standardization; deep phenotyping; longitudinal assessment; real-world applicability.	Guide design, measurement, follow-up, and interpretation.
Operational domains	Clinical; microbiological; histopathological; molecular; immunological; neurological/electrophysiological; imaging; therapeutic outcomes.	Select relevant complementary domains according to the question, not a universal mandatory panel.
Longitudinal integration	Baseline and repeated assessments at prespecified clinically and biologically relevant intervals.	Characterize within-patient trajectories and discordant findings.
Analytical safeguards	Eligibility, confounding, missingness, measurement error, sensitivity analyses.	Address limitations of observational comparisons without presuming causal validity.

The prospective, standardized, and multidimensional structure of DP-RWE does not, by itself, eliminate the methodological limitations inherent to observational research. Potential sources of bias, including selection bias, confounding, missing data, and measurement error, should therefore be considered according to the therapeutic question, study design, and data structure [9,17]. When DP-RWE is used to compare therapeutic regimens or address causal questions, appropriate design and analytical strategies should be prespecified to address these limitations. However, no single comparative or causal-inference method is a constitutive requirement of the framework.

In comparative observational studies using DP-RWE, detailed phenotyping does not in itself remove selection bias, confounding by treatment indication, or systematic measurement error (Table 2). Eligibility, treatment assignment mechanisms, time zero, exposure definitions and outcomes should be prespecified. Depending on the study design and available data, multivariable adjustment, propensity-score methods, inverse-probability weighting and sensitivity analyses may be appropriate. Missing-data patterns and losses to follow-up should be documented and evaluated. Residual and unmeasured confounding may persist; DP-RWE is not intrinsically a causal-inference method.

Table 2. Potential sources of bias and methodological safeguards for observational applications of DP-RWE.

Potential limitation	Implication	Possible Mitigation
Selection bias	Differences in eligibility and recruitment	Prespecified eligibility; transparent recruitment and comparison of baseline characteristics.
Confounding by indication	Prognosis influences choice of treatment	Record indications and prognostic factors; consider adjusted analyses, propensity scores and sensitivity analyses.
Missing data and attrition	Incomplete tests and long-term follow-up	Document missingness and loss; assess plausibility of missing-data assumptions; sensitivity analyses.
Measurement error	Variability across laboratories and observers	Standardized protocols, quality control and reproducibility assessments.
Causal overinterpretation	Residual and unmeasured confounding	Avoid causal claims unsupported by the design and its assumptions.

DP-RWE should therefore be understood as a flexible methodological framework rather than a fixed protocol or a substitute for established study designs. Its application may range from the prospective longitudinal evaluation of a single therapeutic regimen to comparative observational investigations, with the selection of phenotyping domains, assessment schedules, outcomes, and analytical methods determined by the therapeutic question. The framework is intended to increase the biological and clinical resolution of therapeutic evaluation while preserving the characteristics of real-world clinical conditions and explicitly acknowledging the methodological limitations of observational evidence [9,17]. The conceptual, methodological, and empirical foundations that informed the development of DP-RWE are examined in the following section.

4. Supporting Foundations of the DP-RWE Framework

The development of the DP-RWE framework was informed by converging conceptual, methodological, and empirical foundations from the broader biomedical literature and from more than two decades of longitudinal and multimodal research in leprosy. Its individual components are not, in themselves, novel: deep phenotyping, real-world evidence, prospective longitudinal cohorts, standardized data collection, and multidimensional clinical and biological assessment have each been applied in different research contexts. The distinctive contribution of DP-RWE lies in the explicit integration of these established components into a disease-specific, treatment-centred methodological framework for the prospective and longitudinal evaluation of therapeutic regimens in leprosy under real-world clinical conditions. The foundations informing this integration can therefore be considered at three complementary levels: conceptual foundations, provided principally by DP and RWE; methodological precedents, represented by prospective longitudinal and multidimensional research platforms developed in leprosy and other chronic diseases; and empirical foundations, derived from leprosy studies demonstrating the complementary information provided by different clinical and biological domains over time.

At the conceptual level, DP-RWE draws on two established and complementary approaches. DP emphasizes the precise and comprehensive characterization of phenotypic abnormalities and provides the conceptual basis for examining disease and therapeutic response across multiple clinical and biological dimensions [10]. RWE, in turn, provides the conceptual and methodological basis for generating evidence from data relating to patient health status and/or healthcare delivery collected under real-world conditions, with increasing emphasis on data fitness, appropriate study design, and prespecified analytical planning [9,17]. DP-RWE brings these perspectives together around a prespecified therapeutic question, while adding a disease-specific, prospective, longitudinal, and treatment-centred structure tailored to the biological and clinical complexity of leprosy. Several established research platforms and longitudinal cohort initiatives provide methodological precedents for individual components of this integration. Their principal characteristics, methodological contributions, and relevance to the development of DP-RWE are summarized in Table 3.

Table 3. Methodological Precedents and Their Contributions to the Development of the Deep Phenotyping Real-World Evidence (DP-RWE) Framework.

Methodological Precedent	Disease/ Context	Main Methodological Characteristics	Contribution Relevant to DP-RWE	Distinction from DP-RWE
INFIR Cohort [11,12]	Leprosy	Prospective longitudinal cohort; standardized clinical and neurological assessment; nerve function testing; neurophysiological and laboratory measurements.	Demonstrates prospective, standardized, longitudinal integration of complementary measures to characterize neuropathy and reactions.	Designed primarily to investigate prediction, detection, and pathogenesis of neuropathy and reactions rather than multidimensional evaluation of antimicrobial therapeutic regimens.
RePORT International [13]	Tuberculosis—international network	Prospective observational research platform; harmonized protocols; standardized clinical data and biological specimen collection; longitudinal follow-up.	Demonstrates the feasibility of harmonized prospective cohorts integrating clinical information and biological specimens across research settings.	Developed primarily to support tuberculosis biomarker and translational research rather than a disease-specific framework for multidimensional therapeutic evaluation in leprosy.
RePORT-Brazil [14]	Tuberculosis—Brazil	Prospective multicentre observational cohort; standardized longitudinal clinical characterization; treatment-period assessments and post-treatment follow-up within a harmonized research network.	Provides a national example of implementing standardized prospective longitudinal research in a chronic infectious disease within the RePORT network.	Developed for tuberculosis research and its specific scientific objectives rather than as a modular framework centred on multidimensional evaluation of antimicrobial therapeutic regimens.
BADBIR [15]	Psoriasis	Prospective pharmacovigilance registry; standardized longitudinal clinical data; long-term monitoring of treatment exposure, effectiveness, and safety.	Illustrates structured generation of longitudinal real-world evidence for long-term therapeutic effectiveness and safety.	Registry-based therapeutic surveillance without the predefined multidomain biological and neurological phenotyping proposed in DP-RWE.
PSORT [16]	Psoriasis	Stratified-medicine research programme integrating detailed clinical phenotyping with biological and genomic investigation of treatment response.	Illustrates integration of clinical and biological characterization to investigate heterogeneity of therapeutic response.	Developed for treatment stratification and biomarker discovery in psoriasis rather than longitudinal multidimensional evaluation of antimicrobial regimens.

Table 3. *Cont.*

Methodological Precedent	Disease/ Context	Main Methodological Characteristics	Contribution Relevant to DP-RWE	Distinction from DP-RWE
DP-RWE Framework (proposed)	Leprosy therapeutic evaluation	Prospective, longitudinal, modular, disease-specific, and treatment-centred framework integrating selected clinical and biological domains under real-world clinical conditions.	Integrate Standardization, Deep Phenotyping, Longitudinal Assessment, and Real-World Applicability around a prespecified therapeutic question.	Operational domains and assessment schedules are selected according to the therapeutic question; the framework may evaluate a single regimen or compare regimens and does not require any single comparative or causal-inference method.

INFIR, Nerve Function Impairment and Reactions; RePORT, Regional Prospective Observational Research for Tuberculosis; BADBIR, British Association of Dermatologists Biologics and Immunomodulators Register; PSORT, Psoriasis Stratification to Optimise Relevant Therapy. These initiatives are methodological precedents rather than validations of DP-RWE. The precedents summarized here contributed individual methodological elements relevant to DP-RWE; they are not presented as equivalent frameworks or as hierarchical comparators. DP-RWE is proposed as a modular framework, and not all operational domains are required in every study.

As summarized in Table 3, these methodological precedents demonstrate that several components incorporated into DP-RWE are already feasible in prospective and longitudinal research. The INFIR cohort established the value of standardized longitudinal assessment integrating clinical, neurological, neurophysiological, and laboratory measures in leprosy [11,12], whereas RePORT International and RePORT-Brazil demonstrated the feasibility of harmonized prospective cohort infrastructures combining standardized clinical characterization, longitudinal follow-up, and biological investigation in tuberculosis [13,14]. In chronic inflammatory disease, BADBIR and PSORT further illustrate how longitudinal real-world clinical data and detailed biological characterization can contribute to the evaluation of treatment safety, effectiveness, and heterogeneity of therapeutic response [15,16]. These initiatives were developed for different diseases and research objectives and should not be regarded as earlier versions of DP-RWE. Rather, they provide methodological precedents for individual components that DP-RWE explicitly brings together within a disease-specific, treatment-centred, modular framework for multidimensional therapeutic evaluation in leprosy.

Although deep phenotyping, prospective cohorts and real-world evidence are established approaches, DP-RWE proposes their explicit integration around a prespecified therapeutic question in leprosy. Table 4 distinguishes this proposed integration from the established contributions and limitations of its constituent approaches.

The empirical foundations informing DP-RWE also emerged from the progressive integration of complementary clinical and biological approaches in leprosy research. Over more than two decades, longitudinal and multimodal investigations from our group have addressed different dimensions of disease expression and progression, including peripheral nerve involvement and primary neural leprosy, subclinical neurological abnormalities, neurophysiological patterns, structural nerve changes assessed by ultrasonography, serological and molecular markers, and individual risk of disease development [12,18–24]. Although these studies were conducted to answer distinct clinical and research questions and were not designed as DP-RWE studies, collectively they demonstrated the complementary information that can be obtained from different phenotyping domains and the importance of longitudinal assessment in capturing biological and clinical changes that may not be adequately represented by a single measure. This accumulated empirical experience progressively informed the conceptual development of the DP-RWE framework.

Table 4. Comparison of established methodological approaches and the proposed DP-RWE framework: contributions, potential benefits, and limitations.

Methodological Approach	Established Contribution	Additional DP-RWE Proposal	Potential Benefits and Limitations
Deep phenotyping	Detailed multidimensional characterization	Selection and longitudinal integration of question-relevant domains for therapeutic evaluation	Potential biological resolution; costly, complex and not sufficient for causal inference.
Prospective cohorts	Prespecified follow-up and repeated measurements	Treatment-centered integration of complementary clinical and biological trajectories	Temporal detail; susceptible to attrition and confounding.
Real-world evidence	Evidence from routine clinical care	Structured deep phenotyping within real-world therapeutic investigation	Broad applicability; variable data quality and confounding.
DP-RWE (proposed)	Integrative methodological framework, not a new epidemiological design	Explicit modular, prospective, longitudinal, treatment-question-centered integration	Potential interpretive value remains to be tested; resource and analytic limitations persist.

The empirical rationale for DP-RWE becomes particularly relevant in therapeutic evaluation, where different dimensions of treatment response and long-term outcomes may not be adequately represented by a single clinical or laboratory endpoint. Under real-world clinical conditions, systematic assessment of adverse drug reactions has demonstrated differences in the safety profiles of multidrug therapeutic regimens used in leprosy [4], while investigation of suspected treatment failure has required the integration of clinical evolution with bacteriological, histopathological, serological, and molecular findings [5]. Additional investigations of therapeutic failure have further demonstrated the value of combining complementary clinical and biological information when persistent disease activity is suspected after treatment [6]. At the post-treatment level, systematic evidence on leprosy relapse indicates that recurrence may occur after variable and sometimes prolonged intervals, reinforcing the importance of sufficiently long follow-up when late therapeutic outcomes are under investigation [7]. These studies were not conducted within the DP-RWE framework and do not constitute its validation. Rather, they provide empirical observations that informed the methodological rationale for prospectively selecting and longitudinally integrating complementary domains according to the therapeutic question being investigated.

A published case–control study by Dornelas et al. (2024) provides an empirical illustration of complementary measurements in suspected leprosy treatment failure but does not represent a prospective validation of DP-RWE [5]. Table 5 distinguishes the reported findings and methods from their potential use in a future prospective DP-RWE investigation.

Table 5. Published multidimensional evidence from Dornelas et al. (2024) and its potential prospective application within DP-RWE [5].

Component	Published Evidence: Dornelas et al. (2024) [5]	Proposed Prospective DP-RWE Application
Study design	Case–control investigation of 40 patients with suspected treatment failure and 40 controls.	Prospectively define eligibility, treatment exposure and follow-up; do not reinterpret retrospective evidence as framework validation.
Clinical assessment	Clinical suspicion and characterization of treatment failure.	Standardize baseline and serial clinical outcomes.
Histopathology	Histopathological examination contributed to multidimensional assessment.	Use of serial histopathology was justified by the therapeutic question.
Bacteriology	Bacillary assessment complemented other findings.	Track bacteriological trajectories using prespecified measurements.
Serology	Anti-PGL-I serology assessed as a complementary marker.	Study longitudinal immunological changes with explicit limitations.
Molecular testing	Molecular detection contributed complementary evidence.	Use quantitative qPCR where appropriate; DNA persistence is not proof of viability.
Interpretation	Complementary findings were evaluated in relation to suspected failure.	Prespecify interpretation of concordance and discordance.
Methodological safeguards	Case–control design does not establish prospective causal performance.	Plan selection safeguards, missing-data procedures and comparative analyses.

Taken together, these conceptual foundations, methodological precedents, and empirical observations provide the scientific basis that informed the formulation of DP-RWE. Deep Phenotyping contributes the rationale for comprehensive multidimensional characterization, RWE situates evidence generation within real-world clinical conditions, prospective longitudinal research platforms demonstrate the feasibility of standardized follow-up and integration of complementary data, and leprosy studies illustrate the clinical and biological value of examining different dimensions of disease and therapeutic response over time. DP-RWE synthesizes these elements into an explicitly articulated, disease-specific, treatment-centered, and modular methodological framework for therapeutic evaluation in leprosy. This synthesis provides a foundation for prospective application and future evaluation of the framework, rather than evidence that DP-RWE itself has already been prospectively validated.

To illustrate the operational application of DP-RWE, Table 6 outlines a hypothetical prospective comparison of two therapeutic regimens for multibacillary leprosy. The example covers eligibility, baseline characterization, modular selection of phenotyping domains, follow-up, outcomes and analytical safeguards. Annual post-treatment assessments and pro-

longed follow-up for late relapse are illustrative, informed by Nascimento et al. (2022) [25], rather than universal requirements.

Table 6. Hypothetical application of DP-RWE to a prospective comparison of two therapeutic regimens for multibacillary leprosy.

Methodological Component	Hypothetical DP-RWE Application
Therapeutic question and groups	Compare effectiveness and safety of reference regimen A and investigational alternative regimen B in eligible multibacillary patients.
Participant selection	Prespecify eligibility for both regimens, prior treatment, classification, comorbidities and prognostic factors; record reasons for treatment choice.
Baseline	Dermatoneurological examination, bacteriological index, disability, comorbidities and question-relevant complementary investigations.
Phenotyping domains	Modular selection of clinical, microbiological (smear), histopathological (biopsy where indicated), molecular (quantitative qPCR), immunological (anti-PGL-I ELISA), neurological/electrophysiological (examination and nerve conduction studies), imaging (nerve ultrasound) and therapeutic-outcome domains.
During treatment	Prespecified periodic assessment of clinical, bacteriological and neural response, adherence, adverse events and treatment modifications.
Treatment completion	Integrated assessment distinguishing completion of prescribed treatment from individual clinical and bacteriological resolution.
Post-treatment follow-up	Annual dermatoneurological assessments, additional tests as indicated and prompt reassessment when clinically warranted; extended follow-up, illustratively at least 10 years, for late relapse outcomes.
Outcomes	Clinical and bacteriological response, safety, nerve function and disability; prespecify criteria distinguishing insufficiency, failure, relapse and drug resistance.
Analysis and interpretation	Address confounding by indication, loss to follow-up and missing data; interpret discordant domains jointly without equating persistent *M. leprae* DNA with viability or failure.

Implementation across healthcare settings requires attention to infrastructure, workforce, diagnostic technologies, costs and participant burden. However, fixed essential, intermediate and advanced phenotyping packages determined by local resource availability could institutionalize unequal scientific standards for populations affected by a histori-

cally neglected disease. Domains should instead be selected according to the therapeutic question and the relevance of each measure. Referral networks, shared laboratories, and health-system strengthening may support access to necessary investigations. Economic and operational feasibility should be assessed using proportional criteria comparable to those applied to other therapeutic research designs, including randomized trials, without presuming DP-RWE to be less costly or superior.

DP-RWE does not assume a universal hierarchy among clinical, histopathological, microbiological, molecular, immunological and neurological domains. Each measures a different dimension of disease and may follow a distinct temporal trajectory. Discordance between clinical improvement and persistent laboratory or instrumental abnormalities should neither automatically be equated with treatment failure nor dismissed. Persistent *M. leprae* DNA alone does not demonstrate bacillary viability; persistent electrophysiological or imaging abnormalities may reflect residual neural damage. Prespecified primary and secondary outcomes should follow the therapeutic question, without imposing a fixed hierarchy of phenotyping methods.

The proposed framework is informed by longstanding multidimensional longitudinal practice at specialized services, including CREDESH/HC-UFU. Its contribution is to formalize the selection, standardization and integration of such established assessments around explicit therapeutic questions. Prospective evaluation of DP-RWE as a formal framework should assess feasibility, reproducibility across teams and centres, completeness and quality of data, participant burden, and the additional interpretive value of integrating selected domains. Existing clinical and scientific experience should not be conflated with formal prospective or multicentre validation of the framework.

5. Conclusions

This Perspective introduces DP-RWE as a prospective, longitudinal, modular, disease-specific, and treatment-centered methodological framework for multidimensional therapeutic evaluation in leprosy under real-world clinical conditions. By integrating the established concepts of DP and RWE around four core principles: standardization, deep phenotyping, longitudinal assessment, and real-world applicability, DP-RWE provides a structured approach for prospectively selecting and longitudinally integrating clinical and biological domains according to a prespecified therapeutic question.

DP-RWE is intended to complement, not replace, RCTs. Its potential contribution lies in providing a structured methodology for investigating therapeutic effectiveness, safety, biological response, neurological outcomes, treatment failure, relapse, and other relevant outcomes when multidimensional and prolonged evaluation under real-world clinical conditions is scientifically informative. The framework does not prescribe a fixed set of tests, technologies, assessment schedules, or analytical methods, and its prospective structure does not eliminate the limitations inherent to observational evidence. Rather, methodological choices should remain appropriate to the therapeutic question, study design, population, available data, and intended interpretation.

The conceptual foundations, methodological precedents, and empirical observations reviewed in this Perspective informed the formulation of DP-RWE but do not constitute prospective validation of the framework. Its next methodological step is therefore prospective application in clearly defined therapeutic studies, followed by evaluation of its feasibility, reproducibility, analytical performance, and ability to generate clinically and biologically informative evidence across different therapeutic questions and settings. Such evaluation will determine the contribution of DP-RWE to future therapeutic research in leprosy and whether elements of the framework may also be informative in other chronic infectious diseases facing similar challenges in long-term therapeutic evaluation.

Author Contributions: I.M.B.G. conceptualized the DP-RWE methodological framework and was responsible for its methodological development. I.M.B.G. wrote the original draft of the manuscript. B.d.C.D. contributed to the critical review and refinement of the methodological framework. I.M.B.G. and B.d.C.D. contributed to the review and editing of the manuscript and approved the final version. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable. This Perspective presents a conceptual methodological framework and does not report original research involving human participants, human data, or human biological specimens. The previously published studies discussed in the manuscript were conducted under their respective ethics approvals, as reported in the original publications.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article. All empirical studies discussed in this Perspective have been previously published and are cited in the manuscript.

Acknowledgments: The authors express their sincere gratitude to the clinical, administrative, laboratory, and multidisciplinary teams of the National Reference Center for Leprosy and Sanitary Dermatology (CREDESH), including the Laboratory of Molecular Pathology and Biotechnology (Lab. PMBIO), for their longstanding commitment to patient care, clinical follow-up, and research in leprosy. The authors also acknowledge the staff of the Pathology Unit at the Hospital de Clínicas, Federal University of Uberlândia (HC-UFU/HU Brasil), for their technical contributions to the histopathological investigations conducted over the years. The accumulated clinical and research experience of these multidisciplinary teams contributed to the scientific environment from which the conceptual development of the DP-RWE framework emerged. During the preparation of this manuscript, the authors used ChatGPT (GPT-5.6) to assist with English writing correction and figure creation only. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BADBIR	British Association of Dermatologists Biologics and Immunomodulators Register
CREDESH	Centro de Referência Nacional em Dermatologia Sanitária e Hanseníase (National Reference Center for Sanitary Dermatology and Leprosy)
DP	Deep Phenotyping
DP-RWE	Deep Phenotyping Real-World Evidence
ENMG	Electroneuromyography
FDA	Food and Drug Administration (United States)
INFIR	ILEP Nerve Function Impairment and Reactions Cohort Study
MDT	Multidrug Therapy
NTDs	Neglected Tropical Diseases
PGL-I	Phenolic Glycolipid-I
PSORT	Psoriasis Stratification to Optimize Relevant Therapy
qPCR	Quantitative Polymerase Chain Reaction
RCTs	Randomized Controlled Trials
RePORT	Regional Prospective Observational Research for Tuberculosis
RePORT-Brazil	Regional Prospective Observational Research for Tuberculosis—Brazil
RWD	Real-World Data
RWE	Real-World Evidence
WHO	World Health Organization

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