THE PROTECT PROTOCOL

A FRAMEWORK FOR INTEGRATING BRAIN HEALTH INTO OVERDOSE RESPONSE SYSTEMS

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Forward

When I was in my early twenties, I lost my closest friend to what the toxicology report deemed to be an opioid-related death. For years I wrestled with a question the report couldn't answer: was it an accidental overdose, or an intentional suicide? I have spent much of my professional life sitting with that ambiguity, working simultaneously in overdose prevention and suicide prevention, two fields that turned out to be less separate than I had imagined.

Before they died, my friend had experienced multiple overdoses. By the time I returned to visit one summer, they had lost their housing and moved back in with their mother, who was herself living with opioid addiction. I believe they later died on her supply. At the time, I noticed that something felt different about them; slower, harder to reach...but I chalked it up to time and distance. It was only years later, after working directly alongside people with substance use disorder in frontline services, that I understood what I had actually been witnessing: the signs of overdose-related brain injury, quiet and gradual and entirely unnamed by anyone around them.

What strikes me most, in retrospect, is not my own failure to notice, it is that there was no one else around to notice either. My friend was isolated, precariously housed and living in an environment where the drugs that would kill them were already present. Cognitive decline can be gradual enough to escape detection even by those who are close; in the absence of stability, community and safe housing, it escapes detection entirely. No system measured it. No clinician flagged it after an overdose and asked whether they felt different than before, slower to think, harder to organize, more easily overwhelmed. The post-overdose period can involve a neurological haze lasting weeks or months, subtly reshaping how a person thinks and plans. Because it is gradual and because those most affected are often the most isolated, it goes unnamed, by systems, by communities and by the individuals experiencing it themselves.

This last point has stayed with me: many people living with overdose-related cognitive impairment do not know that is what they are experiencing. They know something is harder than it used to be. But the language of brain injury, with its implication of something measurable, treatable and deserving of accommodation, is not available to them, because the systems around them are not offering it.

When I moved into direct service work, I encountered this pattern repeatedly. People cycling through crises, missing appointments, discharged from treatment for non-compliance, unable to articulate their own needs, were not failing for lack of motivation. They were being held to standards their injured brains could not meet, inside systems that had never been designed with them in mind. I also learned that the people who understand these dynamics most clearly are those who have lived them. Any framework that addresses overdose-related brain injury without being built in genuine partnership with people with lived and living experience of substance use is, at some level, repeating the same mistake.

I no longer wrestle with what killed my friend. I understand now that their death was the endpoint of a process that had been underway for years, a gradual neurological and social collapse, accelerated by housing instability, shaped by an environment saturated with opioids and invisible to every system that might have intervened. This report is an attempt to build a framework capable of seeing that process, naming it and interrupting it. It is offered in their memory.

Executive Summary

The Invisible Aftermath of Overdose

Canada's overdose crisis is most often measured in deaths. What remains largely unseen is the far larger population of people who survive. Between 2016 and 2025, more than 53,000 Canadians died from drug overdoses. Over the same period, an estimated 1.1 to 1.6 million non-fatal overdose events occurred, each one a potential brain injury caused by oxygen deprivation, disrupted blood flow, or the direct toxic effects of drugs on brain tissue.

For many survivors, these are not isolated events. Repeated overdoses produce cumulative neurological harm that is often subtle, undiagnosed and untreated. The capacities most commonly affected, memory, judgment, impulse control and emotional regulation, are precisely those required for recovery, stability and safety. Conservative estimates suggest that hundreds of thousands of Canadians and likely more than one million, are living with some degree of overdose-related brain injury, most of it invisible to systems designed for acute emergency response rather than long-term cognitive care.

What makes this particularly difficult to address is that many of those affected are unaware that anything neurological has changed. Cognitive decline following repeated overdose can be gradual, unfolding across months or years rather than appearing suddenly. The post-overdose period itself can involve a neurological haze lasting weeks, quietly reshaping how a person thinks, plans and engages with the world. Without someone present to observe the change, without a system designed to screen for it and without language to name it, the decline goes unrecognized, by clinicians, by communities and by the individuals experiencing it themselves.

A System Built for the Wrong Problem

Overdose-related brain injury is not a secondary complication, it is central to both overdose risk and recovery failure. Brain injury both results from and contributes to high-risk substance use, creating a self-reinforcing cycle: each overdose risks further neurological damage and that damage increases vulnerability to the next overdose.

Current overdose response systems are not designed to interrupt this cycle. They are built on an implicit assumption of intact cognition, the capacity to retain information, follow instructions, self-regulate behaviour and sustain motivation over time. When people with brain injury cannot meet these expectations, their difficulties are routinely misread as non-compliance, lack of readiness, or treatment resistance. The result is discharge from programs at precisely the moment individuals most require accommodation and support.

Treating substance use disorder without recognizing cognitive impairment fundamentally limits what existing interventions can achieve. This is not a failure of effort or compassion. It is a misalignment between system design and neurological reality, one that this report is designed to address.

The PROTECT Protocol: A Learning Health System

The PROTECT Protocol is a learning health system framework, one in which care delivery and knowledge generation are integrated. The model responds to the gap that separates the generation of clinical evidence from its application in practice. PROTECT is designed to close that gap, and is organized around five pillars:

Pillar	Function	Primary Role
PROTECT-ED	Education and Prevention	Builds brain health literacy and workforce capacity to enable early recognition of overdose-related brain injury
PROTECT-ID	Identification and Surveillance	Makes brain injury visible through cognitive screening, biomarkers and data infrastructure
PROTECT-RX	Therapeutic Interventions	Prevents and addresses brain injury through tiered neuroprotective and restorative interventions governed by GRADE-rated evidence
PROTECT-LIFE	Response and Recovery	Ensures overdose response and recovery systems are redesigned around the cognitive needs of survivors
PROTECT-NET	Governance and Accountability	Governs learning, evaluation, equity oversight and integration of evidence across all pillars

Evidence-Driven Implementation

PROTECT deploys interventions according to their level of evidentiary support, rated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework and the Oxford Centre for Evidence-Based Medicine (CEBM) hierarchy, two internationally recognized and complementary standards for assessing evidence quality and the strength of clinical recommendations. Four tiers govern deployment readiness:

Tier	Evidence Standard	Deployment Decision
Tier 1	GRADE Moderate–High; CEBM Level 1–2	Immediate implementation with embedded real-world effectiveness research. Evidence is primarily from analogous populations (acquired brain injury, cardiac arrest neuroprotection, harm reduction); indirectness is documented and monitored per GRADE criteria.
Tier 2	GRADE Low–Moderate; CEBM Level 2–3	Pilot trials required to confirm effectiveness in overdose-specific populations before broader rollout.
Tier 3	GRADE Very Low; CEBM Level 3–4	Feasibility testing at select sites required before broader investment is committed.
Tier 4	Investigational	Formal Phase I–III clinical trials required before any deployment is considered.

Two conditions apply uniformly across all tiers:

- Equity review is a prerequisite for Tier 1 deployment. Before any intervention scales, evidence must confirm it does not produce harm across population subgroups defined by Indigenous identity, race, gender, geography, housing status and substance use disorder severity. Where evidence for a specific subgroup is thin or absent, deployment in that group is deferred and designated as a Tier 2 research priority.
- Interventions that do not meet predefined thresholds for safety, effectiveness, or equity at any stage are discontinued and resources reallocated. All findings, including negative and null results, are reported publicly within six months of completion.

Anticipated Outcomes

PROTECT is designed initially as a targeted intervention for high-risk overdose survivors, with planned scale-up as evidence accumulates. Anticipated outcomes across the pilot phase (Years 1–3) include:

- Routine cognitive screening embedded in post-overdose care pathways, reaching a meaningful proportion of annual overdose emergency presentations
- Integrated acquired brain injury and substance use disorder care pathways operating at pilot scale
- Formal recognition of overdose-related brain injury in Canadian clinical guidelines and policy frameworks
- Measurable reductions in repeat overdose presentations and improvements in treatment retention, with specific targets confirmed through pilot-phase evaluation

Longer-term outcomes (Years 3–10) include system-level integration, sustained workforce competency and transition from structured pilot to documented standard of care, subject to stage-gate performance thresholds and mandatory three-year evidence reviews defined in Chapter 5.

Governance, Accountability and Equity

PROTECT is governed by a multidisciplinary Steering Committee with compensated lived-experience leadership. Decisions are made quarterly using predefined criteria covering safety, effectiveness, feasibility, equity, ethics and community acceptance. Equity safeguards are embedded throughout the framework.

The Case for Action

Every year without an integrated brain health response to the overdose crisis has real consequences: thousands of deaths, hundreds of thousands of emergency responses and tens of thousands more people acquiring untreated brain injury that current systems are not designed to see, name, or address.

The question is not whether Canada can afford to integrate brain health into overdose response. It is whether Canada can afford not to. Overdose is not only a toxicological emergency, it is a neurological crisis with lasting, often unrecognized consequences. Recognition alone is insufficient. Neuroprotective care must be operationalized at scale, in genuine partnership with the communities most affected.

PROTECT provides the framework, the evidence strategy and the governance structure to do so.

1. Overview

1.1 Introduction

Current responses to the overdose crisis are built around a consequential omission: brain injury. Overdose-related brain injury both drives and results from high-risk substance use, creating a cycle that existing systems are not designed to interrupt. Survivors frequently sustain neurological damage from oxygen deprivation and toxic drug exposure, damage that impairs cognition, judgment, impulse control and emotional regulation. These injuries are often invisible, undiagnosed and untreated, yet they fundamentally shape behaviour, treatment engagement and ongoing overdose risk.

What makes this especially difficult to address is that many people living with overdose-related cognitive impairment are not aware that anything neurological has changed. Cognitive decline following repeated overdose can be gradual, unfolding over months or years rather than appearing suddenly after a single event. The post-overdose period itself can involve a neurological haze that persists for weeks, subtly reshaping how a person thinks, plans and relates to the world. Without someone present to observe the change, without a system designed to measure it and without language to name it, the decline goes unrecognized, by clinicians, by communities and by the individuals experiencing it themselves. Isolation, which is both a cause and a consequence of substance use disorder, compounds this invisibility profoundly.

As a result, many people cycle repeatedly through emergency care, treatment attempts, relapse and re-presentation, despite substantial investment in prevention and recovery services. This pattern reflects not a failure of effort or compassion, but a fundamental misalignment between how systems are designed and the neurological realities of the people they serve. Overdose response and treatment systems are built on an implicit assumption of intact cognition: the capacity to retain information, follow complex instructions, self-regulate behaviour and sustain motivation over time. When people with brain injury cannot meet these expectations, their difficulties are frequently misread as non-compliance, lack of readiness, or treatment resistance. The outcome is predictable: recurrent overdose, inefficient use of resources and missed opportunities to prevent further neurological harm.

Correcting this misalignment requires more than clinical innovation. It requires that systems be redesigned in genuine partnership with people who have lived and living experience of substance use, including those who have moved into recovery. The people who understand most clearly where systems break down are those who have navigated them with a brain injury that nobody named.

1.2 Policy Recognition and the Paradigm Shift

Across multiple jurisdictions, health authorities and policymakers are beginning to formally acknowledge what frontline experience and emerging evidence have long suggested: brain injury resulting from repeated overdose is a significant clinical and system-level issue. Recent policy guidance in several jurisdictions recognizes that existing overdose and substance use responses are insufficient to address the intersecting realities of substance use, mental health conditions and acquired brain injury (ABI), neurological damage caused by events after birth, such as oxygen deprivation or toxic exposure, rather than by hereditary or congenital conditions.

This recognition reflects a meaningful departure from frameworks that treat overdose as an isolated acute event rather than a source of cumulative neurological harm. A growing consensus

among researchers, clinicians and public health authorities holds that the overdose crisis can no longer be adequately characterized as a supply-side or toxicological emergency alone, it is a neurological crisis with enduring consequences, requiring evidence-driven, long-term models of care.

1.3 Brain Injury, Overdose and the Cycle of Harm

A growing body of evidence shows that the relationship between non-fatal overdose and acquired brain injury is bidirectional. Overdose-related oxygen deprivation and neurotoxicity produce measurable cognitive impairments; at the same time, pre-existing cognitive vulnerability, including executive dysfunction and prior brain injury, substantially increases the likelihood of high-risk substance use and subsequent overdose (1–4). This dynamic has been described as a vicious cycle of neuropathological, cognitive and behavioural sequelae of repeated opioid overdose (5). Each overdose event risks further damage to the brain systems that govern harm reduction and recovery, memory, attention, executive function and impulse control, increasing vulnerability to the next (6, 7).

Critically, this cycle is largely self-concealing. The very cognitive capacities most needed to recognize a problem, seek help and navigate toward care are precisely those most likely to be compromised. People experiencing overdose-related cognitive decline are often the last to know and existing systems are rarely designed to tell them.

1.4 Population-Level Impact and Unrecognized Morbidity

Cognitive impairment among people who use drugs is common yet profoundly underrecognized. Systematic reviews estimate prevalence at around 30%, with some studies reporting rates as high as 80% among individuals with a history of prior overdose (4, 8). Despite this burden, routine cognitive screening remains rare across overdose response, treatment and harm reduction.

This gap has systemic consequences. Individuals with unrecognized brain injury are less likely to benefit from standard interventions, more likely to disengage from care and more likely to experience repeat overdose (5). Approximately 15% of overdose survivors experience another overdose within one year, with a substantial proportion occurring within the first 30 days (9). Each additional overdose compounds neurological risk: evidence suggests that prior overdose exposure contributes meaningfully to recurrence risk, though the precise mechanisms and their relative contributions remain an active area of research (10, 11).

The cumulative scale of this burden is substantial. For every overdose death, an estimated 20 to 30 people survive a non-fatal event, each representing a potential episode of hypoxic or toxic brain injury (7, 13, 14). Repeated overdoses produce progressive neurological harm affecting memory, judgment, impulse control and emotional regulation, capacities essential for recovery, safety and long-term stability. Conservative estimates suggest that hundreds of thousands of people across affected jurisdictions are living with some degree of overdose-related brain injury, much of it undiagnosed and unsupported.

This constitutes a substantial hidden burden of disability: a neurological aftermath of the overdose crisis that current health systems, designed primarily for acute emergencies, are ill-equipped to recognize, assess, or treat. Overdose-related brain injury is not a marginal concern.

1.5 Mechanisms of Injury: Hypoxia, Neurotoxicity and Damage

Overdose-related brain injury arises through multiple pathways. Opioids, particularly high-potency synthetic opioids such as fentanyl, suppress respiratory function, leading to oxygen deprivation (hypoxia) and reduced blood flow to the brain (16, 17). Brain regions with high energy demands, including the hippocampus and prefrontal cortex (central to decision-making and impulse control), are especially vulnerable. Even brief hypoxic episodes can initiate neuronal injury; repeated or prolonged events risk permanent structural damage (18, 19).

Beyond hypoxia, many substances exert direct toxic effects on the brain. Opioids and stimulants such as methamphetamine can trigger neuroinflammation, oxidative stress and cell death, disrupting the brain's capacity for repair and adaptation (3, 20, 21). These processes compound over time (22). The pattern of cumulative injury from repeated non-fatal overdose mirrors that seen in repetitive traumatic brain injury, where successive insults, even individually mild, drive progressive cognitive decline (4,7).

1.6 Cognitive and Behavioural Consequences

The cognitive effects of overdose-related brain injury are broad, persistent and clinically significant. Executive dysfunction, including impaired decision-making, reduced impulse control, diminished cognitive flexibility and working memory deficits, is particularly prominent (15, 16, 25, 26). Memory impairments affect the ability to learn, retain and apply information, including harm reduction strategies and treatment plans (7, 26). Slowed processing speed and difficulties with sustained attention further limit participation in conventional treatment models (3).

These cognitive changes are frequently accompanied by emotional dysregulation, reduced motivation, altered social cognition and personality changes, all of which complicate engagement with care and place additional strain on social support networks (5). Critically, these impairments actively amplify overdose risk: executive dysfunction undermines harm reduction capacity, memory deficits erode safety learning and impaired inhibitory control increases impulsive risk-taking (27, 28). When cognitive barriers to participation are misread as non-compliance or lack of motivation, the result is often discharge from programs at precisely the moment individuals most require accommodation and support (29). The person is failed twice: first by a system that did not screen for brain injury and second by one that punishes its consequences.

1.7 Overdose-Related Brain Injury as a Syndemic and Equity Issue

Overdose-related brain injury does not occur in isolation. It is embedded within a broader syndemic, a cluster of interacting epidemics that reinforce one another under conditions of social inequality, encompassing substance use, mental health conditions, trauma, poverty, homelessness, infectious disease and criminalization (30). These forces interact and compound one another, with disproportionate impact on Indigenous peoples, racialized communities and people experiencing structural marginalization (31).

Brain injury both arises from and deepens these structural vulnerabilities. Cognitive impairment reduces people's capacity to navigate service systems, maintain housing, manage benefits and advocate for their own care, deepening marginalization and increasing exposure to high-risk drug environments. Housing instability is particularly significant: the absence of safe, stable housing removes the environmental conditions most necessary for neurological recovery, while simultaneously increasing proximity to unregulated drug supplies and reducing access to consistent care. Structural inequities, in turn, heighten the risk of repeated overdose.

2. Theory of Change: Why Existing Systems Fail and How PROTECT Responds

2.1 Starting Point: A Crisis Within a Crisis

The overdose crisis has generated an enormous public health response, in harm reduction, treatment, emergency services and policy. Yet despite sustained investment across all of these domains, the cycle of overdose, treatment failure and repeat overdose continues.

This report argues that the explanation for this persistence is not insufficient effort or inadequate resources. It is that the systems responding to the overdose crisis have been built around a flawed model of who they are serving. That model assumes that the people arriving at emergency departments, entering treatment programs and engaging with harm reduction services have essentially intact cognitive function. For a substantial proportion of overdose survivors, these assumptions are wrong. And the consequences of designing systems around assumptions that do not hold are predictable, costly and ultimately deadly.

2.2 The Causal Chain: How Brain Injury Drives the Cycle

The theory of change underlying PROTECT begins with a causal chain that the evidence reviewed in Section 1 supports clearly and that existing overdose response systems have largely failed to account for.

Step 1: Overdose causes brain injury. Every non-fatal overdose is a potential neurological event. Opioids, particularly high-potency synthetic opioids such as fentanyl, suppress respiratory function, reducing oxygen supply to the brain. Even brief periods of hypoxia can initiate neuronal injury. Stimulants such as methamphetamine cause direct neurotoxicity through neuroinflammation, oxidative stress and cell death. These are not rare or extreme outcomes. They are the ordinary biological consequences of overdose, occurring across the spectrum of severity.

Step 2: Brain injury accumulates silently. A single overdose may produce subtle neurological effects that resolve partially over time. But repeated overdoses produce cumulative damage, a pattern that mirrors repetitive traumatic brain injury, where successive insults drive progressive cognitive decline even when each individual event seems minor. The brain regions most vulnerable to hypoxic and toxic injury, the hippocampus, prefrontal cortex and basal ganglia, are precisely those governing memory, decision-making, impulse control and emotional regulation. Over time and across multiple overdose events, the damage to these systems compounds.

Step 3: Cognitive impairment goes unrecognized, including by the person experiencing it. This is perhaps the most consequential and least understood link in the chain. Cognitive decline following repeated overdose is frequently invisible, not only to clinicians and systems, but to the individuals experiencing it. This is not a paradox but a neurological reality: the very brain systems most damaged by overdose are those responsible for self-monitoring, insight and awareness of change. A person whose executive function has been progressively compromised may have limited capacity to notice that they are less organized than they once were, slower to process information, more impulsive, or less able to retain what they are told.

Isolation compounds this invisibility profoundly. Cognitive change is most often detected by people who knew someone before, who notice that they seem different, slower, harder to reach. But overdose-related brain injury disproportionately affects people who are socially isolated, unstably housed and disconnected from consistent relationships. There may be no one present to notice the change. The post-overdose haze, a period of neurological disruption that can persist for

weeks or months following an overdose event, may be experienced simply as feeling unwell, without any framework to understand it as a neurological aftermath requiring attention.

Systems do not fill this gap. Routine cognitive screening following overdose is rare. The question "has this person sustained neurological damage from their overdoses?" is almost never formally asked. As a result, an injury that is common, measurable and consequential remains unnamed, in medical records, in treatment plans and in the understanding of the person living with it.

Step 4: Unrecognized impairment leads to system mismatch. When people with overdose-related cognitive impairment encounter health and social service systems, they encounter systems built for someone else. Treatment programs expect participants to absorb complex information in group settings, retain it between sessions and apply it under stress. Housing applications require sustained attention, literacy and self-advocacy. Harm reduction strategies assume the capacity to plan ahead, remember safety information and execute multi-step protective behaviours.

For someone with intact cognition, these demands are manageable. For someone with impaired memory, reduced executive function and compromised impulse control, impairments that may be entirely invisible to both the person and the system, they are frequently insurmountable. The gap between what systems require and what the person can reliably do is not recognized as a design problem. It is interpreted as a personal one.

Step 5: System mismatch is misread as personal failure. Missed appointments are recorded as non-engagement. Difficulty following program rules is documented as non-compliance. Inability to articulate needs clearly is interpreted as lack of motivation or readiness. People are discharged from treatment programs for behaviours that are, in fact, symptoms of the neurological condition the system was meant to address. They are assessed as not ready for housing when they cannot navigate the application process. They are described as resistant to services that were never designed to accommodate them.

This misattribution has consequences beyond the individual. It shapes clinical judgment, influences resource allocation and reinforces systemic assumptions about who can benefit from treatment and who cannot. People with overdose-related brain injury are systematically sorted toward the bottom of service systems, assessed as higher-risk, less compliant and less likely to succeed, by systems that have never screened for the neurological condition driving outcomes.

Step 6: Cognitive impairment increases vulnerability to repeat overdose. Executive dysfunction undermines harm reduction capacity. Memory deficits erode safety learning, a person may be told how to use naloxone, or to avoid using alone and be genuinely unable to retain and apply that information. Impaired impulse control increases risk-taking. Emotional dysregulation reduces the capacity to manage stress and craving. And the treatment failures, housing instability and social disconnection that result from system mismatch themselves increase overdose risk, by deepening isolation, increasing exposure to unregulated drug supplies and reducing the likelihood that someone is present to intervene in a crisis.

Step 7: Repeat overdose compounds neurological damage. Each additional overdose is another potential hypoxic or toxic brain injury event and the brain that sustains it is already compromised. The cycle tightens. Neurological capacity continues to erode. System mismatch deepens. The person becomes progressively harder to reach, not because they are less motivated, but because the cognitive infrastructure required to engage with available support has been further damaged.

2.3 Why Standard Responses Have Not Been Sufficient

It is important to be precise about what this analysis does and does not claim. The harm reduction, treatment and emergency response systems that have developed in Canada over the past two decades have saved lives. Naloxone distribution, supervised consumption services, opioid agonist therapy and post-overdose outreach programs have all made meaningful contributions. The argument here is not that these approaches have failed, it is that they have been operating without a critical piece of the picture.

None of these systems were designed with overdose-related brain injury in mind. None routinely screen for cognitive impairment. None systematically adapt their expectations, materials, or processes to accommodate it. None have governance structures that treat neurological recovery as a care goal alongside abstinence or harm reduction.

As a result, all of them, however well designed and well delivered in other respects, face a structural limit. They can reach people who have enough intact cognitive function to engage with them as designed. They struggle, consistently and predictably, with people whose cognitive function has been compromised by the condition those systems are meant to address. The result is not random variation in outcomes. It is a systematic pattern: the people most severely affected by overdose-related brain injury are the least well served by existing systems and therefore the most likely to cycle through them repeatedly without benefiting.

Addressing this requires not the replacement of existing systems but their upgrade, the integration of brain injury awareness, cognitive screening and neurological accommodation into the infrastructure that already exists. This is precisely what PROTECT is designed to provide.

2.4 The Three Conditions for Change

The causal analysis above points to three necessary conditions for breaking the cycle. PROTECT is organized around all three.

Condition 1: Brain injury must be made visible. Injury that is not named cannot be treated, accommodated, or counted. Making overdose-related brain injury visible requires routine cognitive screening following overdose events, population-level surveillance systems that track neurological outcomes alongside mortality and clinical training that enables workforces to recognize cognitive impairment and respond appropriately. It also requires that the people experiencing cognitive decline be told, in accessible, non-stigmatizing language, what may be happening neurologically and what it means for their care.

Condition 2: Systems must be redesigned around neurological reality. Naming the injury is necessary but not sufficient if the systems surrounding people continue to operate on assumptions of intact cognition. Treatment programs must be adapted, with pacing, repetition, simplified materials and memory supports, to serve people whose cognitive function is compromised. Housing pathways must accommodate the navigation difficulties that cognitive impairment creates. First responders and emergency department staff must understand that the person in front of them may not be able to retain what they are told in the next five minutes. Care coordination must account for the executive function demands it places on clients. These are not accommodations for a small minority, they are design adjustments for a population whose neurological profile has been consistently misunderstood.

Stable, safe housing warrants particular emphasis. Housing instability is both a driver and a consequence of overdose-related brain injury, it increases proximity to unregulated drug supplies, removes the environmental structure that supports cognitive recovery and eliminates the

consistent relationships most likely to detect and respond to cognitive change. A brain injury-informed approach to overdose response is, necessarily, a housing-first approach.

Condition 3: Systems must be built with the people they serve. The people who understand most clearly where overdose response systems break down are those who have navigated them with a brain injury that nobody named. People with lived and living experience of substance use, including those in active use, those in recovery and those moving between both, hold knowledge about what actually fails and what might actually help that no research protocol can fully replicate.

This knowledge has historically been consulted after decisions are made, in the form of advisory input that may or may not be acted on. PROTECT treats it differently: as a design requirement, embedded in governance with genuine decision-making authority. This is not a philosophical position alone. It is a practical one. Systems designed without the people they serve tend to optimize for the system's own logic rather than for the people's actual needs. The pattern of cognitive barriers being misread as personal failures is, in part, a consequence of systems having been built by people who did not experience those barriers firsthand.

2.5 How PROTECT Intervenes at Each Link

The PROTECT Protocol is structured to intervene at every link in the causal chain

At the point of acute overdose response, PROTECT introduces neuroprotective protocols, including extended oxygenation following naloxone administration, that address the neurological emergency occurring alongside the toxicological one, reducing the severity of hypoxic brain injury from the moment of first contact.

In the immediate post-overdose period, PROTECT introduces routine cognitive screening and structured follow-up, creating the opportunity to name the injury, inform the individual, connect them to appropriate care and begin planning for the accommodations they will need.

Within treatment and harm reduction systems, PROTECT introduces program-level adaptations that redesign existing services around the neurological profile of the people they serve, reducing the gap between what systems require and what people with overdose-related brain injury can reliably do.

Across the social systems surrounding recovery, PROTECT integrates cognitive accommodations into housing, justice and employment pathways, addressing the structural vulnerabilities that both produce and are worsened by overdose-related brain injury.

At the population level, PROTECT builds the surveillance, data governance and research infrastructure needed to make overdose-related brain injury visible in the systems that plan and fund care, so that the scale of the problem informs policy rather than remaining hidden within aggregate outcome data.

And across all of these, PROTECT is governed by a structure that places lived and living experience at the centre of decision-making, ensuring that what is built reflects the reality of the people it is meant to serve and is continuously refined on the basis of their experience.

2.6 What Success Looks Like

A successful implementation of PROTECT does not eliminate overdose. It changes what overdose means for the people who survive it and for the systems that encounter them afterward.

It means that a person who presents to an emergency department following an overdose leaves with a documented understanding of their neurological status, a care plan that accounts for their cognitive needs and a peer navigator who knows to check in within 72 hours.

It means that when that person enters a treatment program, the program has been adapted to serve them, with materials they can process, timelines they can meet and staff who interpret missed appointments as a signal to reach out rather than a reason to discharge.

It means that when that person needs housing, the pathway to stable housing does not require a level of bureaucratic navigation that their cognitive impairment makes unreachable.

It means that the data generated by their journey through these systems contributes to a population-level understanding of overdose-related brain injury, informing policy, directing resources and making the invisible visible.

And it means that the people designing and refining these systems include people who have lived this experience, whose knowledge of where the system fails is not incidental to the design process but central to it.

This is the change PROTECT is designed to produce. The sections that follow describe how.

3. The PROTECT Protocol: An Integrated Framework

3.1 Overview

The PROTECT Protocol is a comprehensive, learning health system framework designed to prevent, identify, treat and mitigate overdose-related brain injury across the full continuum of care, from acute emergency response through to long-term recovery. It translates evidence on brain injury mechanisms and outcomes into coordinated action at the clinical, policy and systems levels.

PROTECT is organized around five interconnected pillars that function as a continuous, reinforcing system. Each pillar generates data or delivers interventions that inform the next; PROTECT-NET closes the loop, ensuring that evidence generated across the system is used to continuously refine it.

A principle that runs through all five pillars: the people who understand most clearly where these systems break down are those who have navigated them with a brain injury that nobody named. Meaningful involvement of people with lived and living experience of substance use is not a consultation add-on. It is a design requirement, embedded in governance with real decision-making authority and operationalized through research priority-setting processes consistent with CIHR's Strategy for Patient-Oriented Research (SPOR).

3.2 PROTECT-ED: Education and Prevention

PROTECT-ED builds the knowledge and capacity required for every other pillar to function. Without workforce recognition and public understanding of overdose-related brain injury, screening goes unrequested, accommodations go unmade and cognitive impairment continues to be misread as non-compliance.

Key interventions include multi-community brain health campaigns, peer education programs, provider training across emergency medical services (EMS), emergency departments (EDs), primary care and substance use disorder (SUD) services and school-based neuroeducation targeting adolescents. Embedded implementation science studies are designed as Hybrid Effectiveness-Implementation (HEI) trials, specifically Type 1 hybrids in the Curran et al. typology, which simultaneously test clinical effectiveness while gathering data on implementation processes. This architecture is used deliberately to collapse the sequential model of research-then-implementation that has historically produced multi-decade gaps between evidence generation and practice adoption.

A particular focus of PROTECT-ED is reaching people before and immediately after overdose events, when the opportunity to name what is happening neurologically is greatest and when the window for neuroprotective intervention is still open. All public-facing education materials are designed to be accessible to people experiencing cognitive impairment, using plain language, visual supports and peer-delivered formats that do not assume the literacy or executive function that overdose-related brain injury can compromise.

Expected outcomes: Increased acceptance of screening, treatment and cognitive accommodations; reduced stigma; and improved brain injury knowledge across clinical and community settings.

3.3 PROTECT-ID: Identification and Surveillance

PROTECT-ID makes overdose-related brain injury visible, at the individual level through clinical assessment and at the population level through surveillance and data infrastructure. Injury that goes undetected cannot be treated, accommodated, or counted.

A core challenge this pillar addresses is that overdose-related cognitive decline is frequently invisible to the people experiencing it. Gradual neurological change, unfolding across multiple overdose events over months or years, does not announce itself. Routine cognitive screening after overdose events creates the opportunity to name the injury, inform the individual and begin appropriate planning for accommodations and care.

Key interventions include brief cognitive screening tools (MoCA, BEARNI), regional ABI–overdose registries, point-of-care and laboratory-based biomarker testing and integrated data governance frameworks that incorporate privacy protections and Indigenous data sovereignty principles under OCAP® and the CARE Principles. Together, these initiatives support real-time clinical decision-making, equitable care allocation and evidence-informed policy.

Expected outcomes: Early identification of cognitive impairment; improved risk stratification and treatment matching; enhanced population surveillance; and more informed resource allocation across health systems.

3.4 PROTECT-RX: Therapeutic Interventions

PROTECT-RX encompasses the clinical interventions aimed at preventing, limiting, or rehabilitating neurological injury following overdose. Interventions are deployed according to their GRADE-rated tier of evidentiary support, ensuring that approaches with strong existing evidence are implemented immediately while investigational approaches undergo rigorous evaluation before any broader adoption.

Before any Tier 1 intervention is deployed at scale, a documented equity review confirms that available evidence does not indicate differential harm across subgroups defined by race, gender, housing status, Indigenous identity, geography and SUD severity. Where equity evidence is absent or insufficient for a specific population, deployment in that population is designated as a Tier 2 research priority and proceeds under enhanced monitoring protocols rather than standard rollout.

Key interventions include extended oxygenation following naloxone administration, cognitive rehabilitation, structured exercise, nutritional neuroprotection, occupational therapy, family caregiver support, medication optimization and culturally adapted interventions co-developed with Indigenous communities. Emerging interventions, including post-overdose care bundles, CBD neuroprotection, psilocybin-assisted cognitive recovery and therapeutic hypothermia, are categorized by evidence tier to indicate current readiness and the specific research required before broader deployment.

Expected outcomes: Improved cognitive function across executive skills, memory and attention; improved functional independence; increased treatment engagement; and reduced repeat overdose and post-overdose complications.

3.5 PROTECT-LIFE: Response and Recovery

PROTECT-LIFE ensures that the broader systems surrounding overdose survivors, emergency response, treatment programming, housing, justice and employment, are designed with cognitive impairment in mind rather than implicitly assuming it away.

The animating principle of this pillar is direct: a system that discharges people for not following rules they cannot retain, or denies housing to people who cannot advocate for themselves, is not a system that has reckoned honestly with what overdose-related brain injury does. PROTECT-LIFE asks systems to redesign around the people they serve, rather than expecting those people to meet standards their injuries make unreachable.

Key interventions include structured post-overdose follow-up with peer navigation, program-level ABI adaptations for SUD treatment, updated first-responder and ED protocols, integrated care coordination, peer support networks, supportive housing with cognitive accommodations, vocational rehabilitation, justice system screening and diversion and digital cognitive support tools. Feasibility and implementation studies ensure that interventions are effective, scalable and equitable across populations.

Housing stability deserves particular emphasis. Safe, stable housing is not simply a social determinant of health in the general sense, it is a precondition for neurological recovery. Without it, the environmental conditions required for cognitive rehabilitation are absent and proximity to unregulated drug supplies remains high. A brain injury-informed approach to overdose response is, necessarily, also a Housing First approach.

Expected outcomes: Increased treatment engagement and retention; improved housing and employment stability; reduced justice system involvement; enhanced functional independence; and improved quality of life.

3.6 PROTECT-NET: Learning, Governance and Accountability

PROTECT-NET is the system's memory and conscience. It ensures that brain injury remains visible across time, settings and policy cycles and that what is learned from implementation is systematically used to improve every other pillar.

Key functions include longitudinal tracking of cognitive outcomes using consented minimal datasets; cross-system data linkage spanning EMS, emergency departments, treatment programs and community care; governance structures with compensated lived-experience leadership and ethical oversight; and structured feedback loops operating at four timescales matched to decision urgency, real-time safety monitoring, quarterly clinical effectiveness review, semi-annual workforce assessment and annual strategic evaluation (detailed in Chapter 5).

Lived-experience governance is not symbolic inclusion. People with lived and living experience of substance use hold knowledge about system failures and what actually works that no research protocol can fully replicate. PROTECT-NET embeds this knowledge into decision-making through compensated leadership roles, with genuine authority to shape evaluation priorities, flag equity concerns and inform protocol adjustments in real time. Research priorities are co-developed through a process consistent with CIHR's Strategy for Patient-Oriented Research (SPOR) and PCORI's engagement standards.

4. PROTECT Research and Implementation Framework

4.1 Overview: A Learning Health System Built for Real-World Impact

PROTECT is not a research study that defers action until results are in. It is an integrated implementation and learning platform in which every deployment generates evidence, every challenge informs refinement and every successful intervention becomes a model for scaling.

The framework responds to a specific structural problem identified by both the National Academy of Medicine and the Canadian Institutes of Health Research: on average, 17 years separate the generation of clinical evidence from its consistent application in practice. PROTECT is built to compress this timeline by integrating evidence generation into care delivery from the outset. This is the defining logic of a learning health system, a model in which real-world delivery and knowledge production are simultaneous rather than sequential, governed by shared infrastructure and continuous feedback.

Developed in response to the Canadian overdose crisis, the framework is designed for implementation within Canadian health systems while remaining adaptable to other jurisdictions facing comparable challenges. By Year 5, PROTECT aims to transition from a structured pilot into a documented, evaluated and optimized standard of care.

This framework is underpinned by two appendices and an accompanying technical document:

- **Appendix A** provides a summary overview of the full PROTECT research portfolio, organized by evidence tier, with each study described in terms of its core purpose, study design and the key decision it is designed to inform.
- **Appendix B** provides a summary of the evidentiary basis for each PROTECT intervention, including GRADE and CEBM evidence quality ratings and the directness of existing evidence to overdose populations.

4.2 Research Priority Studies (Appendix A)

Appendix A provides a summary research roadmap for evidence generation across the PROTECT program. Studies are organized by deployment readiness tier, from interventions already supported by strong evidence in analogous populations to those requiring formal clinical trials before any deployment can be considered.

Study Design Architecture

Studies across Tiers 1 and 2 are designed as Hybrid Effectiveness-Implementation (HEI) trials following the typology developed by Curran and colleagues (Implementation Science, 2012):

- Type 1 HEI trials test clinical effectiveness while simultaneously gathering implementation data. These are used for Tier 1 interventions where clinical effectiveness is reasonably established in analogous populations and what is required is confirmation of real-world delivery effectiveness alongside optimization of implementation.
- Type 2 HEI trials test both clinical effectiveness and implementation strategy simultaneously. These are used for Tier 2 interventions where promising evidence exists but overdose-specific validation is required alongside understanding of how to implement effectively.
- Type 3 HEI trials test an implementation strategy while observing clinical outcomes.

Where multiple candidate interventions within a tier are under simultaneous evaluation, PROTECT uses adaptive platform trial designs where feasible. Platform trials, demonstrated most visibly in the RECOVERY trial during COVID-19 and the REMAP-CAP critical care platform, allow multiple intervention arms to be evaluated concurrently within a shared infrastructure, with arms added, modified, or discontinued based on pre-specified interim data criteria. This makes the research program itself responsive to accumulating evidence rather than locked into a predetermined protocol.

Pre-Specified Knowledge Translation Triggers

For each study in **Appendix A**, knowledge translation (KT) triggers are defined in advance, before results are known and registered publicly alongside study protocols. These triggers specify three outcomes:

- Positive triggers: What findings would prompt reclassification of a Tier 2 intervention to Tier 1 and recommendation for broader implementation
- Negative triggers: What findings would warrant discontinuation and reallocation of resources
- Equivocal triggers: What signals would prompt protocol modification and further investigation before any go/no-go decision is made

Modification of pre-specified triggers after study initiation requires documented justification reviewed by the PROTECT-NET Steering Committee and notification to the relevant ethics board. This is not a bureaucratic requirement, it is a safeguard against the selective interpretation of evidence that is well-documented in applied health research.

Pre-Competitive Data Sharing

Where multiple Canadian jurisdictions are simultaneously implementing PROTECT-aligned interventions, PROTECT supports pre-competitive data sharing arrangements that pool evidence across sites. Pooled multi-site data dramatically increases statistical power for Tier 2 validation studies, accelerates feasibility determinations for Tier 3 interventions and enables detection of subgroup effects that individual sites would be statistically underpowered to identify, including equity-relevant differential effects across Indigenous populations, remote communities and other underserved groups.

Tier Descriptions

Studies are organized across four tiers, each mapped to the GRADE and CEBM ratings documented in Appendix B:

- Tier 1 (Strong Evidence, Ready for Deployment): HEI Type 1 evaluations optimizing real-world delivery of interventions supported by GRADE Moderate–High evidence from analogous populations. Examples: peer navigator training, provider education assessment, cluster RCT of ABI treatment adaptations.
- Tier 2 (Promising, Validation Required): HEI Type 2 trials confirming effectiveness in overdose-specific populations. Examples: cognitive rehabilitation pilot RCT, nutritional neuroprotection trial, biomarker validation cohort.
- Tier 3 (Emerging, Proof of Concept): Feasibility studies assessing operationalization in real-world settings. Examples: digital health monitoring tools, housing-integrated cognitive supports, mobile screening units.

- Tier 4 (Investigational, Formal Trials Required): Phase I–III clinical trials for novel interventions. Examples: CBD neuroprotection Phase IIa dose-finding trial, psilocybin-assisted cognitive recovery open-label pilot.

Cross-cutting studies address implementation science and equity impact, ensuring that evidence generation spans not only clinical effectiveness but also scalability and the equitable distribution of benefit across populations.

4.3 Evidence Base and Rationale for Interventions (Appendix B)

Appendix B provides a summary of the scientific justification for each PROTECT intervention, documenting the strength and source of current evidence and the directness of that evidence to overdose populations. Interventions are rated on two dimensions:

- Evidence quality: High, Moderate, Low, or Very Low, rated using GRADE criteria reflecting the volume, consistency, directness, precision and risk of bias across available evidence.
- Overdose evidence directness: Direct, Partial, Indirect, or None, using the GRADE concept of evidence indirectness to reflect how closely existing evidence maps to overdose-specific populations and contexts.

Evidence is graded using both GRADE and the Oxford Centre for Evidence-Based Medicine (CEBM) hierarchy. These frameworks function as decision tools: tier assignments in Appendix A follow directly from the Appendix B evidence ratings. Critically, changes to evidence ratings, triggered by new research findings, accumulating pilot data, or community feedback, automatically initiate a tier reassignment review through PROTECT-NET. Appendix B does not run in parallel with deployment decisions; it drives them.

Full intervention profiles, including mechanisms of action, evidence source narratives, key citations and identified evidence gaps, are provided in the PROTECT Research Technical Supplement. Both Appendix B and the Technical Supplement are living documents, updated quarterly as new findings emerge, pilot data accumulate and community feedback is incorporated.

4.4 How the Appendices and Technical Supplement Work Together

The two appendices and the Technical Supplement address complementary questions at different levels of detail:

- **Appendix B** asks: What does existing science tell us about whether this intervention should work and how strong and direct is that evidence?
- **Appendix A** asks: What research do we need to confirm it works in this specific population, using what study design, at what scale and with what pre-specified finding would change what we do?
- The **Technical Supplement** provides: The full methodological and evidentiary detail required to design, conduct and evaluate that research, including power calculations, statistical analysis plans and go/no-go criteria.

Together, they provide: justification for immediate action on high-evidence interventions; transparent acknowledgement of gaps requiring validation before wider rollout; honest assessment of emerging concepts needing feasibility testing; clear separation between promising ideas and interventions requiring formal trials; and an accountability framework ensuring all clinical decisions are evidence-based with pre-specified triggers for change.

5. PROTECT Evaluation Framework

5.1 Purpose and Design Principles

The PROTECT Evaluation Framework provides a multi-level, decision-linked approach to assessing the effectiveness, equity, safety, feasibility and sustainability of all PROTECT interventions. Unlike traditional evaluation models that report outcomes retrospectively, this framework is embedded directly into program operations, creating continuous feedback loops that inform real-time decision-making, intervention refinement and resource allocation.

The framework is built on four principles:

- Multi-level assessment: Evaluating impact from individual patient outcomes through to system-wide policy change
- Decision-linked design: Every metric connects to a specific go, pause, or stop decision point
- Continuous learning: Feedback operates at multiple timescales matched to decision urgency, from real-time safety monitoring to annual strategic review
- Transparency and accountability: All findings, positive, negative and null, are reported publicly within six months of completion

5.2 Evaluation Domains

PROTECT evaluates nine interconnected domains, each addressing a critical dimension of intervention success. Together, these domains ensure that a clinically effective intervention that worsens equity, disrupts workflows, or proves fiscally unsustainable will be identified and modified or discontinued.

Domain	Key Metrics	Data Sources	Frequency	Stakeholder Accountability	Equity Gate
Clinical Efficacy	MoCA/Trail Making improvement; functional independence; repeat overdose reduction; mortality	Clinical assessments, registries, EMR	Quarterly / Annual	Clinicians; hospitals; health authorities	Yes
Safety and Harm Prevention	Adverse event incidence; harm signals; algorithmic bias incidents	EMR, incident reports, dashboards	Real-time / Annual	Clinicians; governance; ethics boards	Yes
Feasibility and Fidelity	Protocol compliance; time to deliver;	Implementation logs, audits, surveys	Quarterly	Care teams; health authorities	No

	workflow disruption				
Equity and Access	Disparity indices by race, gender, geography, housing, SUD status; coverage of marginalized populations; stigma reduction	Registries, surveys, focus groups, equity audits	Continuous / Annual	National/regional authorities; NGOs	Prerequisite
Workforce Capacity	Training completion; knowledge improvement; observed behaviour change; staff retention	Learning management systems, observation audits	Semi-annual	Clinicians; peer workers; training institutions	No
Policy Impact	Guidelines updated or created; adoption rates; time from evidence to policy	Guideline publications, policy tracking, ministry reports	Annual	Guideline bodies; implementation teams	No
Cost-Effectiveness	Cost per QALY; ICER vs. CDA-AMC threshold; budget impact modelling	Health economics analyses; administrative data	Annual	Health authorities; Ministry of Health; funders	Yes
Research Quality	Study completion and protocol adherence; peer-reviewed publications; negative and null findings reported	Research dashboards, publications, audits	Quarterly / Annual	Researchers; ethics boards; governance body	No
Patient and Lived Experience Outcomes	Patient and caregiver satisfaction; engagement and retention; lived experience participation in governance	Surveys, focus groups, governance records	Annual	Patients; advocacy groups; governance boards	Yes

5.3 Multi-Level Evaluation Structure

PROTECT evaluation occurs simultaneously at four nested levels, ensuring that interventions work for individuals, care teams, organizations and the broader health system.

Level	Focus	Why It Matters
Individual	Patients and clinicians	Individual-level success is necessary but not sufficient. Effective interventions fail if they cannot be consistently delivered to diverse patients by real-world clinicians.
Interpersonal	Care teams	Care is delivered by teams. Interventions must fit into existing team dynamics, communication patterns and workflows to achieve consistent implementation.
Organizational	Health service adoption	An intervention that works at one site but fails across others is a research finding, not a solution. This level identifies barriers to spread.
System	Guidelines and funding	Without policy integration and stable funding, successful programs disappear when project funding ends. This level measures the pathway to permanence.

5.4 Stage-Gate Decision Points

PROTECT uses a stage-gate model in which interventions advance, pause, or stop based on predefined performance thresholds. This prevents two common failures: abandoning promising interventions too early due to implementation challenges and continuing ineffective interventions too long due to sunk costs or institutional inertia.

Each stage gate corresponds directly to specific research studies in Appendix A, ensuring that evaluation drives decisions rather than simply documenting them.

Equity performance is not evaluated in parallel with clinical effectiveness at stage gates, it is a prerequisite for advancement. An intervention that demonstrates clinical effectiveness but produces measurable disparities across population subgroups does not advance through the stage gate. It is modified to address the disparity before proceeding, or, where modification is not feasible, discontinued. This condition applies at every stage and cannot be waived.

Stage	Timeline	Key Thresholds	Decision Options
Stage 1: Pilot and Feasibility	Years 0–2	EQUITY PREREQUISITE MET; then: ≥70% training completion; ≤10% workflow disruption; no severe adverse events; preliminary effectiveness signals	Go: advance to Stage 2 / Pause: modify and retest / Stop: discontinue
Stage 2: Multi-Site Validation	Years 2–5	EQUITY PREREQUISITE MET; then: ≥20% functional improvement vs. baseline; cost	Scale: full implementation / Modify: refine and continue / Stop: discontinue

		per QALY below CDA-AMC threshold; equity gaps <10% across populations	
Stage 3: Sustained Implementation	Years 5–10	≥80% adoption across eligible sites; sustained workforce competence; integration into clinical guidelines; three-year evidence review passed	Full integration: becomes standard of care / Policy alignment: embedded in legislation or regulation

Interventions discontinued at any stage are publicly reported with full rationale and resources are reallocated to higher-performing approaches.

5.5 Feedback Loop Structure

Feedback operates continuously across four timescales:

Real-time: Safety monitoring for adverse events and critical harm signals. Automatic alerts to clinical teams and governance; immediate intervention pause if safety thresholds are exceeded.

Quarterly: Clinical effectiveness dashboards; workflow and fidelity monitoring; equity gap analysis. Rapid-cycle adjustments to protocols and targeted outreach to underserved populations.

Semi-annual: Workforce competency assessments; training effectiveness and knowledge retention. Curriculum updates and peer learning between sites.

Annual: Comprehensive evaluation integrating all domains; stage-gate decisions; policy and guideline integration review; pre-specified KT trigger review. Major strategic decisions and resource reallocation.

5.6 Intervention-Specific Evaluation Matrix

The matrix below provides operational detail on what is measured for each specific intervention and what thresholds determine continuation, modification, or discontinuation. All thresholds are subject to equity prerequisite review before advancement decisions are made.

Pillar	Intervention	Tier	Key Evaluation Metrics	Go/No-Go Threshold
ED	Public Awareness and Brain Health Campaigns	1	Knowledge improvement; stigma reduction; help-seeking behaviour	≥70% knowledge improvement; ≥60% reach of target populations
ED	Peer Education Programs	1	Neuro-literacy scores; self-efficacy; peer competency	≥75% skill acquisition; ≥80% peer retention
ED	Provider Training (EMS, ED, Primary Care,	1	Pre-post knowledge scores; observed practice change; protocol adherence	≥80% training completion; ≥70% observed behaviour

	SUD)			change
ID	Cognitive Screening (MoCA, Trail Making)	1	Screening completion; time to complete; referral appropriateness	≥85% screening completion; ≥90% appropriate referrals
ID	Regional ABI–Overdose Registries	1	Data completeness; inter-rater reliability; data-to-action time	≥90% data completeness; <30 days data-to-action
RX	Extended Oxygenation (post-naloxone)	1	MoCA at 30 and 90 days; functional independence; repeat overdose rates	≥20% cognitive improvement; ≥15% overdose reduction
RX	Nutritional Neuroprotection	2	MoCA scores; blood biomarkers; adherence rates	≥15% functional improvement; ≥70% adherence
RX	Cognitive Rehabilitation	2	Executive function tests; treatment retention; quality of life	≥25% executive function improvement; ≥30% retention increase
RX	Structured Exercise	2	Aerobic capacity; cognitive function; program adherence	≥60% program completion; ≥10% cognitive improvement
RX	CBD Neuroprotection	4	Safety profile; tolerability; preliminary efficacy signals	Phase IIa: safe dose identified; ≥80% tolerability
LIFE	Structured Post-Overdose Follow-Up	1	Patient engagement; treatment connection; repeat overdose	≥70% engagement; ≥50% treatment connection
LIFE	Treatment Program ABI Adaptations	1	Treatment retention; completion rates; cognitive-friendly modifications in place	≥35% retention improvement; ≥90% of sites with adaptations
LIFE	Housing-Integrated Cognitive Supports	3	Housing stability; cognitive support utilization; feasibility	≥50% feasibility threshold; ≥70% resident satisfaction
LIFE	Vocational Rehabilitation with Cognitive Accommodations	3	Employment rates; job retention; earnings	≥30% employment increase; ≥6-month job retention
NET	Workforce Training and Practice Change	1	Training completion; competency assessments; practice adoption	≥85% training completion; ≥75% competency achievement
NE	Ethics, Equity and	1	Governance meeting	≥10 governance

T	Lived Experience Governance		frequency; decision influence; equity gap trends	meetings/year; ≤10% equity gaps
NET	Policy Translation and Clinical Guidelines	1	Guidelines published; adoption rates; time to implementation	≥2 guidelines published; ≥60% adoption within 2 years

5.7 AI Tools in Evaluation

The role of AI-assisted tools within PROTECT evaluation is governed centrally through PROTECT-NET, consistent with the framework's overall approach to AI integration. Within the evaluation context, AI supports five functions: real-time safety monitoring, equity auditing, predictive analytics for high-risk identification, workflow optimization and algorithmic bias detection across all AI tools themselves.

In all cases, AI identifies patterns and generates alerts, human clinical and governance judgment determines response. No AI recommendation executes automatically. All AI tools are subject to annual bias audits, algorithmic transparency requirements and Indigenous data sovereignty protections consistent with OCAP® and the CARE Principles.

5.8 A Living, Learning System with Sunset Provisions

The PROTECT Evaluation Framework is not static. It evolves as interventions progress through evidence tiers, as pilot data accumulate and as implementation contexts change across sites and populations. Its purpose is not to judge PROTECT from the outside but to improve it from within, ensuring that what is learned from every deployment makes the next one more effective, more equitable and more sustainable.

All Tier 1 interventions are subject to mandatory evidence review at three-year intervals. These reviews are pre-scheduled, not triggered by complaint or advocacy and operate on a presumption of rigour rather than incumbency: interventions must continue to meet the evidentiary and equity standards required for their tier, or they are reclassified or discontinued. This sunset provision logic prevents the well-documented failure mode in which interventions that were effective at launch persist beyond their evidence base through institutional inertia or accumulated sunk costs.

As the evidence base for overdose-related brain injury continues to grow, the PROTECT framework will evolve with it, not by drifting from its principles, but by holding to them.

Chapter 6: PROTECT Implementation Framework

This chapter delivers the operational architecture translating PROTECT from a framework document into a functioning system. It is organized in four sections: the socio-ecological implementation matrix (6.1), the phased operational plan covering site selection, Year 1 sequencing, and scale-up logic (6.2), the partnership and funding architecture (6.3), and equity-centred implementation requirements (6.4).

6.1 Socio-Ecological Implementation Matrix

Overdose-related brain injury emerges from intertwined biological, cognitive, social, and structural determinants. Effective implementation requires coordinated action across all socio-ecological levels simultaneously.

The matrix below organizes PROTECT interventions across five levels and three implementation stages aligned with the Chapter 5 stage-gate model. Each intervention carries a tier tag indicating deployment readiness: [T1] deploy immediately with embedded effectiveness research; [T2] pilot trial required before broader rollout; [T3] feasibility testing required; [T4] formal Phase I–III trial required, no deployment outside trial settings.

Level 1: Individual

Stage 1 *(Years 0–2)*

PROTECT-ED: Brain Health Literacy [T1]

- Public education reframing overdose as a neurological emergency, integrated into harm reduction and treatment programs
- Foundational neuroeducation in youth and school health curricula: neuroplasticity, hypoxia vulnerability, early intervention
- Self-management supports (exercise, nutrition, sleep, stress regulation) embedded in treatment

PROTECT-RX: Low-Risk Neuroprotective Supports [T1]

- Optimized oxygenation reinforced in layperson naloxone training
- Nutritional neuroprotection (omega-3s, micronutrients, antioxidants) and structured aerobic activity deployed immediately
- Post-overdose neuroprotective kits distributed through supervised consumption sites, EDs, and outreach programs, containing supplements, hydration tools, neuroeducation materials, and exercise guidelines. Packaging co-designed with people with lived and living experience.

Stage 2 *(Years 2–5)*

PROTECT-ID: Individual Screening and Detection [T1/T3]

- Validated cognitive screening tools deployed in post-overdose care pathways [T1]
- Smartphone-based cognitive supports and digital tracking tools deployed subject to Stage

1 feasibility results [T3]

PROTECT-ED: Sustained Literacy Integration [T1]

- Comprehensive neuroeducation integrated into all addiction treatment programs

Stage 3 *(Years 5–10)*

- Provincial or national neuroprotection curricula embedded across education systems, subject to Stage 2 evidence review [T1]
- Population-level cognitive screening for individuals with repeated overdoses, scaled from validated Stage 1–2 protocols [T1]

Level 2: Interpersonal

Stage 1 *(Years 0–2)*

PROTECT-LIFE: Peer and Family Engagement [T1]

- Peer support training in cognitive accommodation, neurological literacy, and post-overdose impairment recognition
- Family education modules on invisible deficits, emotional regulation challenges, and memory impairment — co-designed with caregivers with lived experience

Stage 2 *(Years 2–5)*

- Peer-led cognitive recovery mentoring programs linked to PROTECT-ID screening results [T1]
- Family-inclusive treatment pathways and structured caregiver support groups, scaled from pilot evidence [T2]
- Brain injury literacy programs in high-risk occupations: hospitality, construction, gig economy, and service industries [T1]

Stage 3 *(Years 5–10)*

- Certification pathways for Brain-Injury-Informed Peer Support Specialists, developed with national peer worker and Indigenous peer worker organizations [T1]
- National family support infrastructure for overdose-related acquired brain injury [T1]

Level 3: Organizational / Service System

- The organizational level is where PROTECT's clinical and service system changes are operationalized. Evidence tier discipline is most critical here: service systems have limited capacity to absorb change, and prematurely deploying insufficiently evidenced interventions risks patient harm and institutional resistance that can undermine well-evidenced components.

Stage 1 *(Years 0–2)*

PROTECT-ID: Screening and Early Detection [T1]

- Brief cognitive screening (MoCA, Trail Making Test, BEARNI) introduced in emergency departments, supervised consumption sites, outreach programs, and withdrawal management
- Point-of-care biomarker pilots (GFAP, NfL, S100B, NSE) initiated at selected EDs as Tier 2 feasibility pilots — not standard deployment [T2]
- Neurological literacy and impairment-recognition training for frontline staff and first responders [T1]

PROTECT-RX and PROTECT-ED [T1]

- Optimized oxygenation protocols post-naloxone activated in all emergency settings; emergency neurology consultation pathways established for severe presentations
- Neuroliteracy training integrated into medical, nursing, social work, paramedic, and psychology professional education; justice system personnel training in cognitive impairment recognition and accommodation

Stage 2 *(Years 2–5)*

PROTECT-ID: Integrated Surveillance and Analytics [T1/T2]

- Regionally scaled biomarker testing linked to electronic health records, subject to Stage 1 pilot results [T2]
- AI-assisted predictive analytics integrating biomarkers, overdose history, cognitive screening, and social determinants — deployed only after external bias validation and equity review [T2]
- Routine cognitive screening integrated into primary care, OAT programs, mental health clinics, and detox facilities [T1]
- Mobile screening units for rural and unhoused populations, deployed subject to feasibility study results [T3]

PROTECT-RX and PROTECT-LIFE [T1/T2/T3]

- OAT-plus-neuroprotection programs combining pharmacotherapy with neuroprotective supplements, screening, and cognitive rehabilitation [T1/T2 by component]
- Post-overdose care bundles piloted at select sites, subject to Tier 3 feasibility results before broader adoption [T3]
- Cognitive-accommodated treatment protocols: simplified materials, repetition-based instruction, low-literacy supports, extended timelines, and reduced administrative burden
- Formalised referral pathways between addiction services and neurorehabilitation centres; ABI-specific vocational rehabilitation programs

Stage 3 *(Years 5–10)*

- PROTECT-ID dashboards embedded within health system workflows; validated biomarker panels in emergency departments; national data standardization with ICD-11 ABI coding for overdose [T1]
- Dedicated clinical pathways and specialised clinics for overdose-related ABI; structural integration of neurorehabilitation into all addiction treatment systems [T1]
- Supported housing designed for cognitive impairment, scaled from Stage 2 housing-integrated cognitive support pilots [T3 to T1 pending evidence]

Level 4: Community

Stage 1 *(Years 0–2)*

- Community-based neuroliteracy training for harm reduction workers, outreach teams, shelter staff, and peer workers [T1]
- Co-design processes initiated with affected communities, including Indigenous-specific processes governed by OCAP® and CARE Principles, to develop locally appropriate delivery models
- Initial overdose-related ABI data reporting at local health authority levels, feeding into regional registry development [T1]

Stage 2 *(Years 2–5)*

- Regional surveillance systems tracking prevalence, geographic clustering, and demographic disparities, with disaggregated data by Indigenous identity, race, gender, housing status, and geography [T1]
- Community hubs offering integrated PROTECT services: cognitive screening, peer support, oxygenation training, kit distribution, and care linkage — model subject to feasibility study before broad rollout [T3]
- Expanded neuroprotective kit distribution through harm reduction sites and peer networks [T1]

Stage 3 *(Years 5–10)*

- Municipal neuro-health strategies integrating brain injury prevention into overdose response and social service planning [T1]
- Community-level resource allocation formally informed by PROTECT-ID regional surveillance data [T1]

Level 5: Structural / Policy

Structural and policy-level implementation determines whether PROTECT survives beyond its pilot phase. Without policy integration, legislative recognition, and sustainable funding infrastructure, well-evidenced programs disappear when project funding ends.

Stage 1 *(Years 0–2)*

- Policy adoption of extended oxygenation standards in provincial emergency services; mandated post-overdose care standards covering oxygenation, cognitive screening, and structured follow-up [T1]
- Provincial or federal recognition of overdose-related ABI as a public health condition; national ICD-11 ABI coding standard for overdose adopted in provincial EMR systems
- Pilot funding secured: cognitive screening, biomarker pilots, neuroeducation, and oxygenation protocol adoption

Stage 2 *(Years 2–5)*

- Public coverage established for validated biomarker testing, neuroprotective supports, and neurorehabilitation — benchmarked against CDA-AMC cost-effectiveness thresholds confirmed in Stage 2 evaluation
- Dedicated CIHR funding stream for overdose-related ABI research established, modelled on existing Institute of Neurosciences, Mental Health and Addiction mandate
- Housing First and case management interventions tailored to cognitive impairment embedded in provincial housing program standards
- Provincial Chief Brain Health Officers established in at least three provinces, with mandate for neuroprotection accountability, intersectoral coordination, and annual public reporting
- National PROTECT Advisory Council constituted with compensated lived-experience majority membership and regional Indigenous representation, reporting to the Public Health Agency of Canada

Stage 3 *(Years 5–10)*

- National PROTECT Strategy embedded in public health legislation, providing a durable mandate beyond project funding cycles
- Universal access to cognitive rehabilitation and brain injury services for overdose survivors established as standard of care in provincial health legislation
- Policy reform addressing syndemic drivers: criminalization, poverty, structural racism, and ongoing health impacts of colonization
- Indigenous-led brain health frameworks supported at national and provincial levels through Indigenous-controlled funding streams

6.2 Phased Operational Plan

The socio-ecological matrix describes what PROTECT does. This section describes how it gets stood up: the site selection criteria, Year 1 operational sequence, scale-up conditions, and knowledge translation infrastructure that moves learning from pilot sites into system-level change.

Site Selection Criteria

Pilot sites are selected through a structured readiness review conducted jointly by the PROTECT-NET Steering Committee and prospective site leads, assessed against six criteria:

Criterion	Operational Definition
Overdose volume	Sufficient annual overdose presentations to generate statistical power for embedded effectiveness studies. Minimum thresholds defined per study in the Technical Supplement.
Harm reduction infrastructure	Functioning harm reduction services providing the relational infrastructure for PROTECT-ID screening and PROTECT-ED outreach.
Workforce readiness	Clinical and peer workforce capacity to absorb Tier 1 training and protocol changes without disrupting core services.
Data infrastructure	Existing or rapidly deployable minimum data standards for PROTECT-NET surveillance and cross-system linkage, including EMR access and consent infrastructure.
Equity representation	Sites collectively represent the demographic diversity of overdose populations — urban and rural, Indigenous and non-Indigenous, housed and unhoused — ensuring Stage 1 learning is generalisable and equity gaps are detectable.
Community and governance readiness	Affected communities have been meaningfully engaged in site selection and have provided informed consent. Sites involving Indigenous populations require formal governance agreements consistent with OCAP®.

Year 1 Operational Sequence

Quarter	Priority Actions
Q1 Months 1–3	Governance activation: Steering Committee constituted with compensated lived-experience leadership; ethics submissions filed; OCAP® governance agreements signed. Site readiness assessments completed. Workforce training for cognitive screening and oxygenation protocols initiated. Neuroprotective kit supply chain established.
Q2 Months 4–6	Tier 1 clinical deployments activated: cognitive screening live in EDs and supervised consumption sites; oxygenation protocols implemented in EMS and ED settings; neuroprotective kits in distribution. PROTECT-ID minimum

	dataset live. First peer navigator cohort trained and deployed.
Q3 Months 7–9	Implementation science monitoring underway: HEI Type 1 fidelity monitoring active; first equity gap analysis conducted; rapid-cycle protocol adjustments made. Tier 2 ethics submissions filed for studies with sufficient baseline data. Community hub co-design processes underway.
Q4 Months 10–12	First quarterly evaluation report published. Stage 1 go/pause/stop review conducted using Chapter 5 thresholds. Findings shared publicly within 30 days. Year 2 plan revised. Tier 2 pilot trials activated where ethics approval obtained.

Scale-Up Sequencing

Three principles govern scale-up from pilot to multi-site to national:

- Early adopter sites generate learning before replication. Tier 1 interventions operate at the first cohort of sites for a minimum of 12 months before activation at additional sites, preventing the common failure of scaling before understanding what made a site successful.
- Scale-up is earned, not assumed. Advancement from Stage 1 to Stage 2 requires equity prerequisite thresholds to be met — not merely clinical effectiveness thresholds. An intervention that works clinically but produces measurable disparities does not advance until the disparity is addressed.
- National scale is a policy outcome, not a program outcome. Transition to standard of care at Stage 3 requires clinical guideline adoption, funding mechanism establishment, and legislative or regulatory embedding. PROTECT generates the evidence required for those decisions; it does not substitute for them.

Knowledge Translation Infrastructure

Evidence generation alone does not close the 17-year research-to-practice gap. PROTECT's KT infrastructure moves findings into practice across four channels:

- Clinical guidelines: PROTECT-NET produces GRADE-based clinical practice guidelines on a rolling basis as evidence accumulates. Target: first guidelines covering oxygenation protocols and cognitive screening standards by end of Year 2.
- Workforce training: KT findings update PROTECT-ED curricula on a semi-annual cycle. All materials are available open-access to Canadian health authorities.
- Policy translation: Structured quarterly briefing cycle delivering implementation evidence to Health Canada, PHAC, and provincial Chief Medical Officers of Health. Policy-relevant KT trigger findings communicated within 30 days of governance review.
- Public reporting: All findings (positive, negative, and null) published within six months of completion on the PROTECT public reporting platform.

6.3 Partnership and Funding Architecture

Partnership Activation Sequence

Stage	Required Partners	Partnership Function
Stage 1 Years 0–2	Pilot site health authorities; harm reduction organizations; Indigenous community governance bodies; CIHR; provincial health ministries; ethics boards	Governance; ethics approval; site readiness; Year 1 clinical deployment; data infrastructure
Stage 2 Years 2–5	Additional health authorities; neurorehabilitation centres; brain injury associations; housing providers; justice partners; academic institutions; PHAC	Multi-site validation; ABI–SUD integration; justice diversion pilots; cost-effectiveness analysis; guideline development
Stage 3 Years 5–10	Health Canada; provincial legislative bodies; CDA-AMC; national Indigenous health organizations; professional colleges; international collaborators	Standard of care integration; legislative embedding; national surveillance; international knowledge exchange

Funding Phasing

PROTECT requires three categories of investment, each drawing on different funder types:

- Implementation funding (Tier 1 deployments): Provincial health authority operating budgets, Health Canada's Substance Use and Addictions Program, and foundation support. Formal Canadian cost-effectiveness modelling is a Stage 1 research output that will strengthen the case for Stage 2 investment.
- Research funding (Tier 2–4 trials): CIHR project grants, SPOR partnerships, and industry partnerships for Tier 4 investigational therapies. The PROTECT research portfolio is structured as a coordinated multi-study program grant application.
- Infrastructure funding (data systems, registries, governance): Sustained multi-year federal and provincial investment, pursued through integration with existing CIHI, provincial EMR, and PHAC surveillance infrastructure rather than parallel systems.

Cost-effectiveness modelling will calculate costs of inaction (recurrent overdoses, long-term disability, justice system involvement, and lost productivity) against implementation costs across all five pillars. Initial modelling using conservative assumptions from the acquired brain injury and harm reduction literature suggests Tier 1 interventions, particularly extended oxygenation and cognitive screening, are likely to achieve favourable incremental cost-effectiveness ratios relative to the CDA-AMC threshold.

Regulatory Pathways

- Health Canada Special Access Program: Applicable to Tier 4 investigational therapies where compassionate access may enable limited trial access before Phase II/III completion.

- Harm reduction exemptions: Federal exemptions under the Controlled Drugs and Substances Act are required in some jurisdictions for supervised consumption and oxygen-first response. PROTECT's policy engagement function includes active support for exemption applications at pilot sites.
- Medical device and AI pathways: AI-assisted tools deployed within PROTECT are subject to Health Canada's Software as a Medical Device (SaMD) framework. PROTECT-NET's AI governance structure is designed to generate the clinical validation and bias auditing evidence required for SaMD classification.

6.4 Equity-Centred Implementation

Equity is a prerequisite that governs PROTECT. The populations bearing the greatest burden of overdose-related brain injury are those whose cognitive impairment is most likely to go unrecognized, whose access to neuroprotective care is most limited, and whose experiences with health systems have most often caused harm. A framework achieving clinical effectiveness without addressing these realities will reproduce, not reduce, existing disparities.

The equity requirements below are not aspirational. They are embedded in governance, evaluation design, deployment prerequisites, and research protocols throughout this document.

Populations Requiring Priority Investment

- Indigenous Peoples: Implementation in Indigenous communities is governed by OCAP® and the CARE Principles, requires formal community governance agreements, uses Community-Based Participatory Research designs for all Tier 2 studies, and is directed by Indigenous-controlled health organizations wherever possible. Indigenous-led brain health frameworks are supported as distinct from, not derivative of, the PROTECT framework.
- People who are unhoused or precariously housed: Housing stability is both a driver of overdose risk and a precondition for neurological recovery. PROTECT's Housing First integration is non-negotiable. Mobile screening and community hub models are designed specifically to reach people who do not access institutional health settings.
- People in rural and remote communities: Telehealth, community health worker models, mobile screening units, and strategic neuroprotective kit distribution are the primary delivery mechanisms where geographic isolation compounds overdose burden and limits specialist access.
- Racialized communities: Culturally safe service delivery, community co-design, and continuous bias monitoring in AI-assisted tools are required throughout implementation, not optional enhancements.
- People experiencing active substance use: PROTECT imposes no abstinence requirements at any point. Neuroprotective care is offered within harm reduction frameworks that respect autonomy and meet people where they are. Cognitive impairment must not become a reason to exclude people from services.

Structural Requirements for Equitable Access

- Cost elimination: All Tier 1 interventions are publicly funded regardless of ability to pay. Cost barriers are deployment failures, not equity gaps to be monitored.
- Low-barrier settings: Interventions are available where marginalized populations access care — harm reduction sites, shelters, outreach, and mobile units — not only in hospitals

or specialized clinics that many individuals avoid due to prior harm, stigma, or practical barriers.

- Cognitive accessibility: All PROTECT-ED materials and clinical tools are designed for people experiencing cognitive impairment. Plain language, visual supports, peer-delivered formats, and low administrative burden are required design features.
- Continuous disparity monitoring: All evaluation data are disaggregated by Indigenous identity, race, gender, housing status, geography, and SUD severity. Equity gaps detected at any evaluation cycle trigger a mandatory protocol review. Equity performance is a deployment prerequisite, not a metric balanced against clinical outcomes.
- Community authority: Affected communities hold decision-making authority in governance structures determining research priorities, evaluation criteria, and protocol adjustments. Compensation for lived-experience leadership is budgeted as core program cost.

7. Risk Management and Governance Framework

7.1 How Evaluation and Risk Management Work Together

PROTECT operates two complementary accountability systems in parallel. The Evaluation Framework (Section 5) measures whether interventions achieve their intended outcomes, asking: *Is this working?* The Risk Management and Governance Framework ensures that no intervention, regardless of its effectiveness, causes harm, violates rights, or erodes public trust, asking: *Is this safe, ethical and acceptable?*

Only interventions that satisfy both frameworks advance to full implementation. This dual approach prevents two common failures: harmful effectiveness, where interventions produce measurable results but damage communities; and safe ineffectiveness, where well-intentioned programs consume resources without producing meaningful benefit.

In practice, the two systems are integrated rather than sequential. The Evaluation Framework operates on quarterly and annual cycles with predefined metrics. Risk management operates continuously, with real-time harm monitoring and immediate authority to pause or stop any intervention. Governance receives input from both, making integrated go, pause, modify, or stop decisions. Stop rules from risk management override positive evaluation findings when harm is detected.

7.2 Acting with Urgency While Managing Risk

PROTECT is designed to move quickly without compromising safety, equity, or public trust. Because overdose-related brain injury is an urgent and evolving crisis, PROTECT does not wait for perfect evidence, but it does not allow unproven or harmful approaches to persist unchecked. Risk is actively managed at every stage through clear decision rules, continuous monitoring and real authority to pause, modify, or stop interventions. Action is timely, learning is rapid and harm is prevented rather than explained after the fact.

7.3 Eight Risk Domains

Every PROTECT activity is continuously assessed across eight core risk domains. Each represents a distinct dimension in which interventions can cause unintended harm, even when clinically effective. No intervention advances on the basis of clinical effectiveness alone; equity, safety, feasibility and community trust carry equal weight.

Domain	Core Question	Red Flags That Trigger Review
1. Safety	Are there signs of harm, adverse events, or unintended consequences?	Unexpected adverse events; safety signals in vulnerable populations; harm patterns not seen in trials
2. Feasibility	Can this be delivered in real-world settings without overloading staff or systems?	Implementation fidelity below 50%; workflow disruptions above 10%; staff burnout signals
3. Effectiveness	Is there credible evidence of benefit?	No improvement after six months; effect sizes below clinically meaningful threshold; benefits only under ideal conditions
4. Equity	Are outcomes, access, or burdens distributed unevenly	Outcome disparities above 20% across demographic groups; geographic access

Domain	Core Question	Red Flags That Trigger Review
	across populations?	barriers; systematic cultural or linguistic exclusion
5. Workforce Impact	Does this support or strain the people delivering care?	Training completion below 70%; staff resistance or moral distress; unsustainable workload increases
6. Resource Value	Is the benefit proportionate to the resources required?	Opportunity cost too high relative to available alternatives; diminishing returns at scale
7. Ethics and Rights	Does this align with consent, dignity and community values?	Coercion or reduced autonomy; privacy violations; community rejection or mistrust
8. Lived Experience Feedback	Do people most affected see this as helpful, safe and acceptable?	Patient or community satisfaction below 60%; reports of stigma or harm; withdrawal of community support

Every quarter, governance reviews a risk dashboard showing status across all eight domains for each active intervention. Green indicators signal the intervention is performing well; yellow indicates monitoring is needed; red triggers immediate review.

7.4 Stage-Gate Decisions

At predefined decision points aligned with the Evaluation Framework's stage-gates, each intervention receives one of four outcomes based on integrated assessment across both frameworks:

Decision	Meaning	Typical Triggers	What Happens Next
Go	Proceed as planned	All eight risk domains green or yellow; evaluation metrics met; no safety concerns	Continue to next implementation phase; maintain monitoring
Pause	Address identified risks before moving forward	One to two domains show yellow flags; additional data needed	Temporary hold of 30–90 days while issues are addressed; resume when resolved
Modify	Redesign to reduce harm or improve feasibility	Feasibility or equity challenges; community feedback requires adaptation	Intervention redesigned, pilot tested and re-evaluated before broader rollout
Stop	Discontinue and redirect resources	Safety concerns; no effectiveness signal; ethical violations; better alternatives available	Immediate discontinuation; resources reallocated; findings published transparently

Stopping is not failure, it is evidence that the system is working. Programs that are never stopped either are not attempting ambitious enough interventions, or are not being honest about what is not working. Over a five to seven year implementation period, some proportion of piloted interventions is expected to be discontinued, freeing resources for approaches that demonstrate clear benefit.

7.5 Stop Rules

An intervention is paused, redesigned, or stopped when evidence meets the following thresholds:

Trigger	Specific Conditions	Review Timeline	Decision Authority
Safety	Serious adverse event attributable to intervention; unexpected mortality increase; pattern of harm in vulnerable population	Immediate (24–48 hours)	Medical Director and Ethics Board
Effectiveness	No meaningful benefit after reasonable trial period; effect size below clinically important threshold; benefits fail to replicate across settings	6–12 months	Governance Steering Committee
Operational Failure	Implementation fidelity below 30% despite support; persistent workflow disruption above 20%; unable to deliver across majority of settings	3–6 months	Implementation Lead and Site Directors
Ethical Violations	Stigma, exclusion, coercion, or punitive use documented; consent violations; privacy breaches	Immediate	Ethics Board, authority to override all other considerations
Equity Harms	Disproportionate harm to specific communities; systematic exclusion of marginalized populations; community withdrawal of support	3–6 months (immediate if harm is severe)	Equity Committee and Lived Experience Council
Loss of Trust	Community rejection; acceptability scores below 40%; evidence of surveillance misuse or criminalization	3–6 months	Lived Experience Council and Governance
Superseded	Better alternatives become available; evidence emerges that intervention is harmful or unnecessary	Ongoing review	Governance Steering Committee

Immediate stops, for safety and ethical violations, can be initiated by any governance member. All other stops require a Steering Committee vote. All stop decisions are documented with full rationale and shared publicly within 30 days, including what was tried, why it was stopped, what was learned and where resources were redirected.

7.6 Continuous Monitoring and Course Correction

Risk management does not wait for quarterly reviews to detect problems. Multiple monitoring loops operate simultaneously at different timescales:

Real-time: Serious adverse events, safety signals, algorithmic bias alerts, privacy breaches. Any serious adverse event triggers an immediate response within 24 hours.

Weekly: Implementation fidelity, workflow disruptions, frontline staff concerns. Fidelity below 60% or disruption above 15% triggers a one-week investigation.

Monthly: Patient complaints, community feedback, early equity warning signals. Satisfaction

below 50% or equity gaps above 15% triggers a two to four week response.

Quarterly: All eight risk domains, stage-gate readiness. Any red flag in the risk dashboard is addressed at the next governance meeting within a maximum of 90 days.

Annual: Comprehensive risk audit, stop rule assessment, independent review, public reporting.

Escalation follows a clear protocol: individual site concerns are resolved at the clinical level within 48 hours; patterns detected across multiple sites are investigated by the implementation team within one week; systemic concerns trigger a governance committee review within 30 days; critical harms result in immediate pause and a Medical Director and Ethics Board decision within 24 to 48 hours.

7.7 Protecting Against Known Harms

PROTECT actively monitors and prevents predictable risks that have emerged in similar initiatives. The following harm prevention protocols are embedded in program design from the outset.

Stigma and exclusion: Cognitive screening is framed as a brain health check rather than deficit identification. Results are stored separately from the main medical record with restricted access. Explicit anti-discrimination language is embedded in all program materials and quarterly audits monitor for exclusionary practices.

Criminalization and surveillance misuse: PROTECT data is explicitly protected from law enforcement, child protection and immigration authority access. No data sharing with justice or enforcement systems occurs without individual consent and legal representation. Registry data is de-identified for research purposes and all data access requests are subject to community oversight.

Algorithmic bias: All AI tools undergo mandatory bias auditing before deployment, with stratified performance reporting across demographic groups. A disparity of 20% or greater triggers immediate algorithm retraining. Clinicians retain the option to override AI recommendations at all times.

Unequal access: Mobile screening units extend reach to encampments and rural areas. All materials are available in translation with cultural adaptation. Peer navigators from affected communities support navigation and all PROTECT interventions are provided at no cost to participants.

Consent and privacy violations: Consent is obtained using plain language materials at a Grade 6 –8 reading level, with a teach-back method requiring participants to explain in their own words what they have agreed to. Data sharing is opt-in rather than opt-out and participants retain the right to withdraw at any time without penalty or loss of services.

Lived experience tokenism: People with lived and living experience of substance use are compensated at the same rates as clinical consultants. Their role is decision-making, not advisory. The Lived Experience Council holds veto authority over interventions affecting the communities they represent and participation is supported through childcare, transportation and trauma-informed meeting environments.

When harm is detected, the response follows five steps: immediate pause of the component causing harm; root cause analysis within 48 to 72 hours; redesign, pilot testing and re-evaluation; transparent reporting to affected communities; and protocol update to prevent recurrence across the system.

7.8 Data Governance

All PROTECT data systems operate under strict governance principles designed to protect individuals, respect community sovereignty and ensure that data serves healing, never punishment or surveillance.

Indigenous data sovereignty (OCAP® and CARE Principles)

For all data involving First Nations, Métis and Inuit peoples, PROTECT implements the following:

Principle	Meaning	PROTECT Implementation
Ownership	Communities own their data	Indigenous health authorities control access to data from their members and hold veto power over research use
Control	Communities control data collection, use and disclosure	Indigenous data governance committees determine acceptable uses; researchers require community approval
Access	Communities have the right to access their data	Real-time dashboards available to Indigenous health authorities with no delays or barriers
Possession	Communities physically possess or securely store their data	Option for data to reside on Indigenous-controlled servers, with backup controlled by communities
Collective Benefit	Data use must benefit the community	Research questions co-developed with communities; results shared before publication; tangible community benefits required
Authority to Control	Communities recognize and govern their data ecosystem	Indigenous representation on all governance bodies with data access; final authority on algorithmic tools
Responsibility	Data stewards are accountable to the community	Annual reporting to communities; complaints escalated to Ethics Board
Ethics	Data governance respects dignity and rights	Cultural protocols embedded; traditional knowledge protected; consent processes respect collective decision-making

Universal data protections (all participants)

- Patients own their data; PROTECT is a temporary steward
- Informed consent uses plain language with teach-back verification; consent is ongoing, not one-time
- Participants may withdraw at any time without penalty or loss of services
- Data is used only for stated purposes; new uses require new consent
- Privacy-preserving methods include de-identification, secure linkage and minimal necessary data collection
- Research datasets are time-limited and destroyed after analysis unless consent for retention is obtained
- Data is never sold or shared with commercial entities

- All research must demonstrate potential community benefit; extractive research is prohibited

Governance structure

A Privacy Officer with independent authority to audit, investigate and stop data practices oversees all data systems. A Data Stewardship Committee, including patients, clinicians, researchers, Indigenous representatives and ethicists, reviews all data access requests. An annual transparency report documents who accessed what data, for what purpose and with what outcomes. Breach protocols require immediate notification, investigation, remediation and public reporting.

7.9 A Culture of Honest Learning

Negative and null results are not failures. They are valuable evidence that prevents wasted resources, protects people from ineffective interventions and redirects effort toward more promising approaches. Treating the absence of a positive finding as something to be hidden or explained away is the actual failure and it is one that PROTECT is explicitly designed to prevent.

PROTECT embeds a culture of honest learning through:

- Public reporting of stopped interventions with full rationale and lessons learned
- Publication of null findings with the same rigour as positive findings
- Governance norms that treat course corrections as routine rather than as crises
- Explicit acknowledgement that "we do not yet know" is an acceptable answer when evidence is genuinely uncertain
- Community safety and dignity as the overriding considerations when evidence and political convenience conflict

This requires institutional courage: the willingness to fund bold experiments knowing some will fail, to stop popular programs when evidence says they are not working and to trust communities with honest information rather than protecting them from it.

7.10 Summary

PROTECT manages risk systematically through clear frameworks, continuous monitoring, real decision authority, proactive harm prevention, robust data protection, full transparency and genuine community power. The result is a system that acts with urgency while maintaining discipline, one that generates evidence while protecting people and learns rapidly while earning trust.

The evaluation and risk management frameworks are complementary, not competing. Evaluation asks: *Is this working?* Risk management asks: *Is this safe and acceptable?* Both must answer yes for any intervention to advance.

8. Conclusion: From Recognition to Action

Across Canada and in jurisdictions around the world, a meaningful shift in understanding is underway. Overdose is increasingly recognized not merely as an acute pharmacological emergency, but as a neurological crisis with lasting consequences. This recognition matters. But recognition alone is not enough.

The evidence reviewed in this report makes a clear and urgent case: overdose causes brain injury, brain injury impairs the cognitive capacities essential for recovery and impaired cognition increases the risk of subsequent overdose. This cycle is self-reinforcing and, without deliberate intervention, self-perpetuating. Every overdose event is also a potential neurological emergency, one that may quietly reshape how a person thinks, plans and navigates the world for weeks, months, or years afterward. Current systems, designed primarily for acute crisis response, are not built to see this. They measure survival, not what survival leaves behind.

What makes this particularly consequential is that the people most affected are frequently the least positioned to name what is happening to them. Cognitive decline following repeated overdose is often gradual and invisible, to the individual experiencing it, to the clinicians treating them and to the systems meant to support them. Isolation compounds this invisibility. In the absence of stable housing, consistent relationships and systems designed to screen for neurological change, brain injury accumulates silently, misread as non-compliance, interpreted as lack of motivation and met with discharge rather than accommodation. The person is failed not once but repeatedly, by systems that were never designed to recognize brain injury.

Correcting this requires more than clinical innovation. It requires a fundamental reorientation of how overdose response systems are designed, away from the implicit assumption of intact cognition and toward frameworks that accommodate the neurological realities of the people they serve. It requires that neuroprotection be operationalized, not merely acknowledged. And it requires that the people with the deepest understanding of where systems fail, those with lived and living experience of substance use, be genuine partners in building what comes next.

The path forward requires coordinated action across multiple sectors:

Researchers must prioritize clinical trials of neuroprotective interventions in overdose populations, validate biomarkers for early injury detection and conduct the longitudinal studies needed to understand long-term cognitive trajectories and recovery.

Clinicians must integrate brain injury screening and neuroprotective protocols into post-overdose care pathways, treating the neurological event, not only the toxicological one.

Policymakers must fund neurorehabilitation services, establish regulatory pathways for promising interventions and shift the orientation of overdose response from containment toward prevention and recovery.

Harm reduction organizations must advocate for and implement brain health approaches within their frameworks, recognizing that harm reduction and neuroprotection are not competing priorities but complementary ones.

Communities with lived and living experience must guide implementation at every stage, ensuring that what is built is equitable, culturally safe and genuinely responsive to the realities of people's lives.

The stakes are clear. Thousands of people survive overdose each year with unrecognized, untreated brain injuries that increase their vulnerability to the next one. Many are young. Many

carry the weight of intergenerational trauma, housing instability and structural marginalization that both deepens their risk and limits their access to care. The science now confirms what frontline experience has long suggested. Policy has begun to acknowledge it.

The task now is to act on it, with urgency, with rigor and with humility.

Appendix A: PROTECT Research Priority Studies

Summary Table

This table provides the research decision architecture for the full PROTECT portfolio. Studies are organized by evidence tier, reflecting the GRADE and Oxford Centre for Evidence-Based Medicine (CEBM) ratings documented in Appendix B. Tier assignments are not administrative categories, they are deployment decisions: the tier assigned to each study determines when and under what conditions the corresponding intervention is implemented, whether it requires pilot validation before scale, or whether it requires formal clinical trial data before any deployment.

Each study is described in terms of its study design and the key deployment decision it is designed to inform. For studies at Tiers 1 and 2, the study design column identifies the Hybrid Effectiveness-Implementation (HEI) trial type following the Curran et al. (2012) typology, which is the design standard for PROTECT's evidence generation strategy (see Chapter 4.2). The HEI typology is used because it generates implementation evidence in parallel with effectiveness evidence, directly addressing the 17-year research-to-practice gap that motivates the learning health system architecture.

For each Tier 1 and Tier 2 study, knowledge translation (KT) triggers, the pre-specified findings that would prompt reclassification, scale-up, or discontinuation, are registered publicly alongside study protocols before results are known. The location of registered KT triggers for each study is documented in the PROTECT Research Technical Supplement.

Full study specifications, including design rationale, sample size, power calculations, timelines, budget estimates, statistical analysis plans, go/no-go criteria and registered KT triggers, are provided in the PROTECT Research Technical Supplement.

Study	Pillar	Tier	Study Design / HEI Type	Key Decision This Study Will Inform
Tier 1, Strong Evidence (Ready for Deployment): HEI trials optimizing real-world delivery; GRADE Moderate–High from analogous populations				
Naloxone + Extended Oxygenation	RX	1	HEI Type 1	Should extended oxygenation be standard protocol following naloxone administration?
Brief Cognitive Screening Validation	ID	1	HEI Type 1	Which screening tool should be standard practice following overdose and at what timing?
Structured Post-Overdose Follow-Up	LIFE	1	HEI Type 1	Which post-overdose follow-up model most effectively supports treatment engagement and reduces repeat overdose?

Treatment Program ABI Adaptations	LIFE	1	HEI Type 2[2]	Should brain injury-informed adaptations be required across substance use disorder treatment programs?
First Responder ABI Training	ED	1	HEI Type 1	Should brain injury training be mandatory for first responders and what form should it take?
Peer Neurological Literacy Training	ED	1	HEI Type 1	Should neurological literacy be a core component of peer worker training and certification?
Public Awareness Campaign Evaluation	ED	1	HEI Type 1	Is neurological framing of overdose effective at reducing stigma and increasing help-seeking at scale?
School-Based Neuroeducation	ED	1	HEI Type 2[2]	Should brain health education targeting overdose risk be embedded in school curricula?
Regional ABI–Overdose Registry	ID	1	Implementation Study	Is systematic ABI surveillance feasible and useful at a regional health system level?
Long-Term Recovery Cohort	ID	1	Longitudinal Cohort	What are the long-term cognitive trajectories, disability outcomes and associated costs for overdose survivors?
Implementation Science Study	NET	1	HEI Type 3	What are the key barriers and facilitators to scaling PROTECT successfully across sites?
Equity Impact Assessment	NET	1	Mixed-Methods Evaluation	Are PROTECT's benefits equitably distributed across populations and where do gaps emerge?
Clinical Practice Guideline Development	NET	1	Evidence Synthesis / KT	How should post-overdose brain injury care be standardised in Canadian clinical guidelines?
Tier 2, Promising (Validation Required): HEI trials confirming effectiveness in overdose-specific populations; GRADE Low–Moderate				
Blood Biomarker Validation Cohort	ID	2	Validation Cohort	Should blood-based biomarkers guide individualised post-overdose care and risk stratification?
AI Risk Prediction Model Development	ID	2	Predictive Model Development[3]	Can AI-supported tools safely and equitably predict cognitive outcomes and repeat overdose risk?
Point-of-Care Biomarker	ID	2	HEI Type 2	Should rapid point-of-care biomarker testing be deployed in

Implementation				emergency department settings?
Cognitive Rehabilitation Pilot RCT	RX	2	HEI Type 2	Should structured cognitive rehabilitation be integrated into substance use disorder recovery programs?
Nutritional Neuroprotection RCT	RX	2	HEI Type 2	Should targeted nutritional supplementation be standard care following overdose?
Structured Exercise for Neuroprotection	RX	2	HEI Type 2	Should supervised exercise programs be recommended as part of post-overdose recovery?
Occupational Therapy for Functional Recovery	RX	2	HEI Type 2	Should occupational therapy be integrated into substance use disorder recovery pathways?
Medication Optimization Protocol	RX	2	HEI Type 2	Should a systematic medication review protocol, including OAT optimisation and anticholinergic reduction, be standard in post-overdose care?
Family Caregiver Support Programs	RX	2	HEI Type 2	Should structured caregiver support be offered to families of overdose survivors with brain injury?
Indigenous-Adapted Interventions	RX / LIFE	2	CBPR / HEI Type 2[4]	What culturally grounded, community-led adaptations of PROTECT interventions are effective and acceptable in Indigenous communities?
Tier 3, Emerging (Proof of Concept): Feasibility studies before broader investment; GRADE Very Low				
Post-Overdose Care Bundle Pilot	RX	3	Feasibility Study	Should bundled neuroprotective interventions be adopted as a coordinated protocol in emergency and post-acute settings?
Mobile Screening Units	LIFE	3	Feasibility Study	Can cognitive screening be feasibly and acceptably delivered in community settings for rural and unhoused populations?
Housing-Integrated Cognitive Supports	LIFE	3	Feasibility Study	Should cognitive accommodations be systematically embedded in supportive housing programs?
Justice System Screening and	LIFE	3	Feasibility Study	Can cognitive screening and triage be feasibly integrated

Diversion				into justice settings to support diversion to treatment?
Digital Cognitive Support Tools	LIFE	3	Feasibility Study	Should digital tools supplement professional rehabilitation services for overdose survivors in recovery?
AI Care Coordination Integration	ID	3	Feasibility Study	Can AI-assisted care coordination safely and equitably enhance service integration for overdose survivors?
ABI–SUD Service Integration Model	LIFE	3	Feasibility Study	Should formal partnerships between brain injury and addiction health systems be adopted broadly?
Tier 4, Investigational (Formal Trials Required): Phase I–III clinical trials before any deployment				
CBD Neuroprotection Phase IIa	RX	4	Phase IIa Dose-Finding RCT	Is CBD safe and tolerable as a post-overdose neuroprotective intervention and what is the optimal dose?
CBD Neuroprotection Phase IIb	RX	4	Phase IIb Efficacy RCT	Does CBD at the optimal dose improve cognitive outcomes following overdose?
Therapeutic Hypothermia Phase I	RX	4	Phase I Safety / Feasibility	Is therapeutic hypothermia safe and feasible in the post-overdose context?
Psilocybin-Assisted Cognitive Recovery Phase I	RX	4	Phase I Open-Label Pilot	Is psilocybin safe and acceptable as a component of cognitive recovery for overdose survivors?

[2] HEI Type 2 is used where both the clinical effectiveness and the implementation strategy require simultaneous evaluation, appropriate where promising evidence exists but the delivery model for this specific population is not yet established.

[3] AI Risk Prediction Model Development follows a predictive model development and external validation design (TRIPOD guidelines) rather than an HEI trial typology, as the primary output is a validated predictive tool rather than a clinical intervention.

[4] Indigenous-Adapted Interventions use a Community-Based Participatory Research (CBPR) approach as the primary design framework, reflecting the requirement that Indigenous communities hold authority over research design, data governance and knowledge translation. The HEI Type 2 component is embedded within the CBPR process, not superimposed upon it. Research priorities, protocols and consent processes are co-developed in accordance with OCAP® and the CARE Principles.

Appendix B: PROTECT Evidence Base

Summary Table

This table summarizes the evidentiary basis for each PROTECT intervention, documenting the strength of existing evidence and the directness of that evidence to overdose-specific populations. Evidence ratings drive tier assignments in Appendix A: the tier assigned to each intervention follows directly from its evidence quality and directness ratings, as detailed in the mapping documented in the PROTECT Research Technical Supplement. Updates to evidence ratings, triggered by new research findings, accumulating pilot data, or community feedback, automatically initiate a tier reassignment review through PROTECT-NET.

Full intervention profiles, including mechanisms of action, evidence source narratives, key citations and identified evidence gaps, are provided in the PROTECT Research Technical Supplement. Appendix B is a living document, updated quarterly as new findings emerge, pilot data accumulate and community feedback is incorporated.

How to Read This Table

Evidence Quality is rated using four levels from the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework. GRADE does not equate evidence quality with study design, study design is a starting point that is upgraded or downgraded based on five factors: risk of bias, inconsistency of results across studies, indirectness of evidence to the population of interest, imprecision of effect estimates and likelihood of publication bias. A well-designed observational study can be GRADE Moderate; a poorly executed RCT can be GRADE Low.

GRADE Level	Meaning
High	We are very confident the true effect is close to the estimate. Evidence typically derives from multiple well-conducted RCTs or very strong observational evidence with no major limitations across risk of bias, consistency, directness, precision and publication bias.
Moderate	We are moderately confident in the effect estimate. The true effect is likely close to the estimate but may be substantially different. Evidence may come from RCTs with some limitations, or from observational studies with consistent, precise results.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different. Evidence typically comes from observational studies with limitations, RCTs with serious limitations, or evidence that is indirect to the population of interest.
Very Low	We have very little confidence in the effect estimate. The true effect is likely substantially different from the estimate. Evidence is typically from case series, mechanistic rationale, preclinical studies, or highly indirect sources.

Overdose Evidence Directness uses GRADE's concept of indirectness to characterise how closely the available evidence maps to overdose-specific populations and contexts:

Directness	Meaning
Direct	Intervention has been tested in overdose populations with outcomes directly relevant to overdose-related brain injury.
Partial	Some evidence from overdose populations exists but gaps remain, either in population coverage, outcome measurement, or follow-up duration.
Indirect	Evidence is established in analogous populations (e.g., acquired brain injury, cardiac arrest neuroprotection, traumatic brain injury rehabilitation, harm reduction) with a logical and documented basis for extension to overdose contexts. GRADE rates this as ‘indirectness’ and treats it as a reason to consider downgrading evidence quality.
None	No human evidence in any directly relevant population. Evidence is preclinical, mechanistic, or from populations with no clear logical basis for extension to overdose-related brain injury.

PROTECT-ED: Education and Prevention

Intervention	Tier	Mechanism in Brief	Evidence Quality (GRADE)	Overdose Evidence (Directness)	Key Evidence Gap
Public Health Messaging (Brain Health Campaigns)	1	Reframing overdose as a neurological emergency reduces stigma and increases help-seeking	Moderate	Indirect	No overdose-specific messaging trials
Peer Education Programs	1	Peer educators deliver neurological literacy to hard-to-reach populations	Moderate	Indirect	Fidelity and reach in overdose populations
Provider Training (EMS, ED, Primary Care, SUD)	1	Workforce training improves recognition, accommodation and referral	Moderate	Indirect	Behaviour change maintenance over time

School-Based Neuroeducation	1	Early brain health education may prevent initiation and support earlier help-seeking	Moderate	Indirect	Long-term prevention outcomes
Implementation Science Study	1	Identifies adoption barriers and facilitators essential for scale-up	High	N/A	PROTECT-specific context

PROTECT-ID: Identification and Surveillance

Intervention	Tier	Mechanism in Brief	Evidence Quality (GRADE)	Overdose Evidence (Directness)	Key Evidence Gap
Cognitive Screening (MoCA, Trail Making, BEARNI)	1	Brief screening identifies impairment requiring clinical accommodation	High	Partial	Optimal timing and frequency post-overdose
Regional ABI–Overdose Registries	1	Systematic data collection enables surveillance and resource allocation	High	Partial	Linkage feasibility across jurisdictions
Data Governance Framework	1	Privacy protections and Indigenous data sovereignty prevent surveillance-related harms	High	N/A	OCAP® implementation in overdose data systems
Population Surveillance Systems	1	Integration with public health surveillance enables real-time monitoring	High	Partial	Real-time data linkage infrastructure

Equity Impact Assessment	1	Continuous monitoring ensures interventions reduce rather than exacerbate disparities	High	N/A	Disaggregated outcome measures in overdose populations
Blood-Based Biomarkers (GFAP, NfL, S100B, NSE)	2	Biomarkers released during brain injury enable objective risk stratification	Moderate	Partial	Overdose-specific thresholds and predictive validity
AI Risk Prediction Models	2	Machine learning identifies patterns predicting cognitive decline or repeat overdose	Moderate	None	Bias auditing; external validation in overdose populations
Point-of-Care Biomarker Testing	2	Rapid biomarker results enable real-time clinical decision-making	Moderate	None	ED feasibility; clinical decision thresholds
Digital Health Monitoring (Apps, Wearables)	3	Continuous monitoring between clinical encounters enables early identification of decline	Low	None	Feasibility; acceptability; cognitive accessibility
AI Care Coordination Integration	3	AI-assisted coordination identifies high-risk cases and improves service efficiency	Low	None	Safety; equity; fragmented system feasibility

PROTECT-RX: Therapeutic Interventions

Intervention	Tier	Mechanism in Brief	Evidence Quality (GRADE)	Overdose Evidence (Directness)	Key Evidence Gap
Extended Oxygenation (10–15 min post-naloxone)	1	Prolonged oxygen corrects brain oxygen debt persisting beyond behavioural recovery	High	Indirect	Optimal duration and delivery in overdose context
Clinical Practice Guideline Development	1	GRADE-based guidelines translate evidence into consistent practice	High	N/A	Overdose-specific neuroprotection guideline development
Nutritional Neuroprotection (Omega-3, NAC, Vitamins)	2	Targeted nutrients reduce oxidative stress and support neurological recovery	Moderate	Indirect	Optimal formulation and timing post-overdose
Cognitive Rehabilitation (Metacognitive, Compensatory)	2	Structured rehabilitation improves executive function and compensatory capacity	Moderate–High	Indirect	Effectiveness in SUD-comorbid populations
Structured Exercise for Neuroprotection	2	Exercise promotes neuroplasticity and improves cerebral blood flow via BDNF upregulation	Moderate	Indirect	Optimal type, intensity and frequency post-overdose
Occupational Therapy for Functional Recovery	2	OT addresses functional	Moderate	Indirect	Integration with SUD treatment pathways

		impairments through compensatory strategies and skill training			
Medication Optimization (OAT, Anticholinergic Review)	2	Optimal OAT dosing and reduced anticholinergic burden improve cognitive and overdose outcomes	Moderate	Partial	Systematic protocol effectiveness in practice
Family Caregiver Support Programs	2	Caregiver education and skills training reduce burden and improve patient outcomes	Moderate	Indirect	Effectiveness with overdose-ABI caregiver population
Indigenous-Adapted Interventions	2	Cultural adaptation is essential for effectiveness and acceptability in Indigenous communities	Moderate	None	Community-specific protocols; CBPR process outcomes
Post-Overdose Care Bundles	3	Bundled interventions may produce synergistic neuroprotective effects	Low	None	Feasibility; synergy vs. component effectiveness
CBD Neuroprotection	4	CBD reduces neuroinflammation and promotes neurogenesis; preclinical evidence promising	Low	None	Human safety; dose-finding; overdose-specific efficacy

Therapeutic Hypothermia	4	Cooling reduces metabolic demand and secondary neuronal injury; strong mechanistic rationale from cardiac arrest and neonatal HIE; operationally complex in overdose context	Low[5]	Indirect	Safety and feasibility in post-overdose populations; operational protocol development
Psilocybin-Assisted Cognitive Recovery	4	Psilocybin promotes neuroplasticity via 5-HT2A agonism; application to overdose-related cognitive recovery is highly speculative	Low	None	Human safety; acceptability; efficacy signal in overdose populations

PROTECT-LIFE: Response and Recovery

Intervention	Tier	Mechanism in Brief	Evidence Quality (GRADE)	Overdose Evidence (Directness)	Key Evidence Gap
Structured Post-Overdose Follow-Up (Peer Navigation)	1	Systematic follow-up improves treatment engagement; peer navigation adds neurological literacy and cognitive accommodation	Moderate–High	Partial	ABI-informed navigation model effectiveness
Treatment Program ABI Adaptations	1	Program-level adaptations improve retention by accommodating	Moderate	Indirect	SUD program-specific adaptation effectiveness

		cognitive impairment			
Enhanced Emergency Response Protocols	1	EMS training in extended oxygenation and neurological assessment improves acute response	Moderate	Indirect	Protocol adherence at scale
Emergency Department Standardised Assessment	1	Standardised protocols improve care consistency and neurological pathway integration	Moderate–High	Indirect	Overdose-specific ED pathway effectiveness
Integrated Care Coordination	1	Case management coordinating across addiction, brain injury, housing and mental health improves outcomes	Moderate–High	Partial	ABI-specific coordination model outcomes
Peer Support Networks	1	Peer support reduces isolation and provides practical strategies for brain injury-informed recovery	Moderate	Indirect	ABI-informed peer support model fidelity
Supported Housing (Brain Injury-Informed)	1	Housing stability is a precondition for neurological recovery; brain injury accommodations extend Housing First	Moderate–High	Partial	Cognitive accommodation effectiveness within Housing First
Vocational Rehabilitation (Cognitive Accommodations)	1	Cognitive assessment, job matching and	Moderate	Indirect	Effectiveness in overdose survivor

		workplace accommodations improve employment outcomes			population
Housing-Integrated Cognitive Supports	3	On-site cognitive accommodations in supportive housing may improve stability and recovery	Low	None	Feasibility; acceptability; outcome measurement
Justice System Screening and Diversion	3	Cognitive screening in justice settings may support diversion to treatment	Low	Indirect	Feasibility; diversion pathway outcomes
Digital Cognitive Support Tools	3	Apps providing reminders and cognitive exercises may augment professional services	Low	None	Acceptability in cognitively impaired populations; accessibility
Mobile Screening Units	3	Mobile units extend cognitive screening to rural and unhoused populations	Low	None	Operational feasibility; screening accuracy in field settings
ABI–SUD Service Integration Model	3	Formal partnerships between brain injury and addiction systems reduce fragmentation	Low	None	Partnership governance; shared protocol development

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