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MNZH MAKE NEW ZEALAND HEALTHY

# Guarantee Scientific Integrity In Informed Consent.


**THE PROBLEM:** The current consent framework does not transparently disclose both therapeutic benefit and potential for serious harm in absolute, comprehensible, and population-relevant terms. In this current system, the good intentions of doctors and medical experts are challenged by poor quality information that undermines the ability of them to communicate absolute risk.

The Medical Council of New Zealand's guidance on informed consent (July 2021) establishes a clear professional obligation on clinicians: patients must understand the risks, benefits, and alternatives of treatment before agreeing to it. Yet in practice, the health system's capacity to achieve genuine informed consent is constrained by deficiencies in evidence quality, transparency, and timely updating of therapeutic data used in routine care. For consent to be valid, patients must be able to approximately judge:

1. *The likelihood that a treatment will meaningfully improve symptoms or prevent deterioration.*
2. *The likelihood that treatment may result in a severe, disabling, or life-threatening event.*

At present, much of the information relied upon by clinicians, including formularies and manufacturer data sheets, lacks transparent citation of underlying studies, clear presentation of absolute risk, or linkage to full trial data and to regulatory submissions. Claims of efficacy are frequently presented without accessible reference to study design, duration, population characteristics, or limitations. Long-term outcome data are often absent or outdated.

***The Nutrition Blind Spot.*** The consent framework overwhelmingly centres on pharmacological or device-based interventions, neglecting the nutritional and metabolic dimensions of illness.

***Case Study: Antidepressants.*** The prescribing of antidepressants illustrates systemic weaknesses with current approaches. Publicly available safety and efficacy summaries consistently lack transparent linkage to trial datasets or regulatory submissions.

**THE SOLUTION:** A credible informed consent framework must convey both therapeutic benefit and potential for serious harm in absolute, comprehensible, and population-relevant terms.

This framework would align public drug information with contemporary standards of evidence synthesis, improve risk communication, and reduce the informational burden placed on patients and clinicians, while ensuring methodological rigor and transparency. To meet a reasonable public-interest standard, consent materials must include:

- Age- and sex-specific data on drug efficacy: symptom relief, prevention of escalation, hospitalisation, or mortality.
- Age- and sex-specific harm data: incidence, severity, withdrawal effects, hospitalisations.
- Transparent comparison of pharmacologic vs. nutritional or lifestyle alternatives.
- Absolute risk framing: expressed per 100 treated, including NNT and NNH.
- Recognise nutrient-based treatment safety profile. From mild tolerability to rare toxicities.

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# MNZH POLICY RECOMMENDATIONS:

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1. **Foundational Health Assessment Prior to Pharmacotherapy**. Implement routine screening for key nutrient insufficiencies and metabolic markers where clinically relevant before initiating long-term pharmacotherapy.

2. **Integrate Nutrition as First-Line Strategy Where Appropriate.** Offer structured dietary and nutritional interventions as first-line options for conditions such as prediabetes, type 2 diabetes, and people diagnosed with brain-related conditions, where evidence supports benefit and risk is low.

3. **Mandatory Disclosure of Absolute Benefit and Harm Data.** Require clinicians to provide age- and sex-stratified NNT/NNH tables and discuss tapering or discontinuation considerations where relevant.

4. **Transparent Formularies and Data Sheets.** Require national formularies and Medsafe data sheets to include: Original trial citations (with DOIs), study durations and population characteristics; clear disclosure of evidence gaps; and linked access to systematic reviews and regulatory evaluations.
    a. ***Evidentiary Dating and Population Relevance.*** All efficacy and safety claims must disclose: Year(s) of pivotal trials, trial duration and follow-up, population inclusion/exclusion criteria, limitations in youth-specific or pregnancy data.
    b. ***Placebo Integrity:*** Regulators must require full disclosure of placebo composition in trials. Placebos containing co-formulants (e.g., microcrystalline cellulose, magnesium stearate, or partial actives) distort both safety and efficacy signals. A genuinely inert comparator (physiologic saline, for example) is essential to interpret drug-specific effects.
    c. ***Data transparency must be statutory, not voluntary*****.** Regulatory placeholders for 'commercial confidentiality' should never override public health interests.
    d. ***Independent, Publicly Accessible Safety Summaries*****.** Develop New Zealand-specific, publicly accessible safety summaries independent of manufacturer packaging materials.

5. **Trial Decoding Tools:** Clinicians require concise, publicly verifiable tables showing *absolute event counts* and *study-level metadata*.

6. **Public-Interest Evidence Synthesis.** Leverage modern analytic tools to:
    - Extract absolute risk and adverse event frequencies.
    - Identify subgroup effects.
    - Detect methodological limitations.

- Reconcile discrepancies between journal publications, registries, and regulatory submissions.
- Outputs must be transparent, reproducible, and open to independent scrutiny.

7. **Technical recommendation: implement a statutory Five-Year Evidence Reappraisal Cycle** for all medicines listed on the Pharmaceutical Schedule, prioritising high-utilisation agents and those prescribed to vulnerable or physiologically distinct populations (children, adolescents, pregnant or lactating women, and the elderly). Each cycle should generate a publicly accessible, version-controlled living monograph meeting the following specifications:

a. ***Systematic evidence integration.*** Conduct structured evidence synthesis incorporating:

- Regulatory assessment reports (e.g., FDA, EMA, TGA, Medsafe, NICE, Health Canada);
- Clinical study reports, trial registries and post-marketing data;
- Pharmacovigilance databases, including spontaneous reports and cohort analyses; and
- Peer-reviewed literature and meta-analyses.

Evidence identification and extraction should follow PRISMA-consistent methodology. However, over-reliance on PRISMA guidelines when undertaking a meta-analysis is cautioned. PRISMA is a reporting guideline, not a methodology or quality guarantee. It improves transparency but does not ensure methodological rigor.

b. ***Absolute risk–benefit quantification.*** Report all outcomes using standardised, patient-interpretable metrics:
   - absolute risk difference,
   - number needed to treat (NNT),
   - number needed to harm (NNH), and include
   - incidence per 100 or 1,000 treated.

Where data permit, stratify by:

- Age categories (including <12, 12-18 and 18–24) thereafter by decade, and sex;
- Pregnancy trimester and postpartum period; and
- Co-morbidity and concomitant pharmacotherapy.

c. ***Methodological transparency and bias assessment***. Reappraisals must explicitly report:
   - Study design, duration and randomisation details;
   - Inclusion/exclusion criteria and attrition;
   - Run-in protocols and potential enrichment biases;
   - Selective outcome reporting and publication bias; and
   - External-validity limitations and population representativeness.

Evidence certainty should be graded using a recognised framework (e.g., GRADE), supplemented by clear narrative interpretation of uncertainty.

d. ***Traceability, version control and reproducibility.*** Every claim within formularies and Medsafe data sheets must link directly to its primary source, including:
   - Full citation and publication date;
   - Population characteristics; and

- Outcome definitions and statistical methods.

A version-controlled audit log must record all amendments. While this would have been technically difficult a decade ago, current database infrastructure and open-source workflows now make reproducible, end-to-end audit trails entirely feasible.

e. ***AI-assisted evidence synthesis with expert validation (5-year reappraisal cycle).*** Artificial intelligence tools, including natural-language processing and large-language-model-based analysis, may assist by:
    - Extracting outcome and adverse-event frequencies and absolute risk data (per-100 treated).
    - Identifying age-, sex-, and comorbidity-specific subgroup effects.
    - Detecting methodological anomalies (e.g., unblinding, outcome switching, short-duration enrichment).
    - Reconciling discrepancies among journal publications, trial registries, clinical study reports, and regulatory dossiers.

To ensure that the evidence is scientifically robust and trustworthy, outputs must be:

- ✓ Publicly released for critique by an independent, multidisciplinary panel with demonstrated research expertise spanning pharmacology, clinical medicine, epidemiology/biostatistics, pharmacovigilance, and nutrition/metabolic & brain health.
- ✓ Reproducible via documented workflows, including versioned code, extraction rules, inclusion and exclusion decisions, and full data provenance linking each extracted datum to its source.
- ✓ Accompanied by uncertainty quantification, including confidence intervals where appropriate, sensitivity analyses (e.g., publication bias, missing data assumptions, risk-of-bias scenarios), and disclosure of data gaps (e.g., absent long-term harms or under-represented populations).
- ✓ Contestable, allowing external analysts to rerun pipelines, propose corrections, and trigger transparent amendments with audit-tracked reasoning. True independence depends not on who performs validation, but on whether validators can examine the complete evidentiary record.

# BACKGROUND TO THIS POLICY

Informed consent, in its public-interest sense, requires more than listing risks; it requires helping patients understand the nature and severity of harm and the realistic choices available to them.

The exercise of clinical judgement is therefore not only technical but moral. Clinicians are in a position of relative power and treatments do hold potential to harm. Four ethical principles: beneficence, non-maleficence, respect for autonomy, and justice have historically guided clinicians in decision-making (for information on these principles see Appendix [1]).

Applying ethical and regulatory principles consistently, including attention to cumulative exposure, vulnerable groups, reversibility, and monitoring needs, supports patient autonomy while ensuring safety. In practical terms, this means enabling patients to address nutrient deficiencies

where appropriate, receive medical treatment where appropriate, while clearly communicating when the potential severity or unpredictability of harm from competing and complementary interventions may place them in different risk categories which either does or does not requiring professional oversight.

## (i) CASE STUDY: ANTIDEPRESSANTS

In Section [A] below MNZH provides the example of the New Zealand-based information available to doctors, psychiatrists, nurse practitioners and patients for reviewing the safety and efficacy of a group of commonly prescribed antidepressants.

Publicly available safety and efficacy summaries frequently lack transparent linkage to trial datasets or regulatory submissions. Long-term outcomes, withdrawal risks, and youth-specific data remain insufficiently presented.

The prescribing of antidepressants illustrates the systemic weaknesses that prevent clinicians and patients from forming an accurate picture of absolute risk.

The case study, discussed below, is not a 'unique to psychiatry' issue, instead it is indicative of broader informational gaps across medicines and devices.

## (ii) NUMBERS NEEDED TO TREAT VERSUS FREQUENCY OF ADVERSE EVENTS

However, the good intentions of clinicians can be undermined by poor quality information which does not enable clinicians to appropriately judge absolute risk. Measures such as the number needed to treat (NNT) and the number needed to harm (NNH), expressed per 100 or 1,000 treated individuals, provide clinicians and patients with a clearer understanding of the likely balance between benefit and harm. Equally important is distinguishing mild tolerability effects associated with nutrients from rare but serious toxicities that may be more likely to be experienced from pharmaceutical compounds and biologic medicines.

Public-good decision making should equip patients to distinguish between:

*(1) manageable, early-signal effects that can guide self-correction, and*

*(2) harms that escalate unpredictably or require clinical supervision*.

Yet unfortunately and critically, clinicians and patients are seldom provided with:

- Absolute risk reductions (e.g., per 100 treated).
- Numbers needed to treat (NNT) to prevent severe symptoms, hospitalisation or death.
- Numbers needed to harm (NNH) for serious adverse outcomes.
- Subgroup-specific data by age and sex and baseline metabolic status.

Without this information, consent risks becoming procedural rather than substantive.

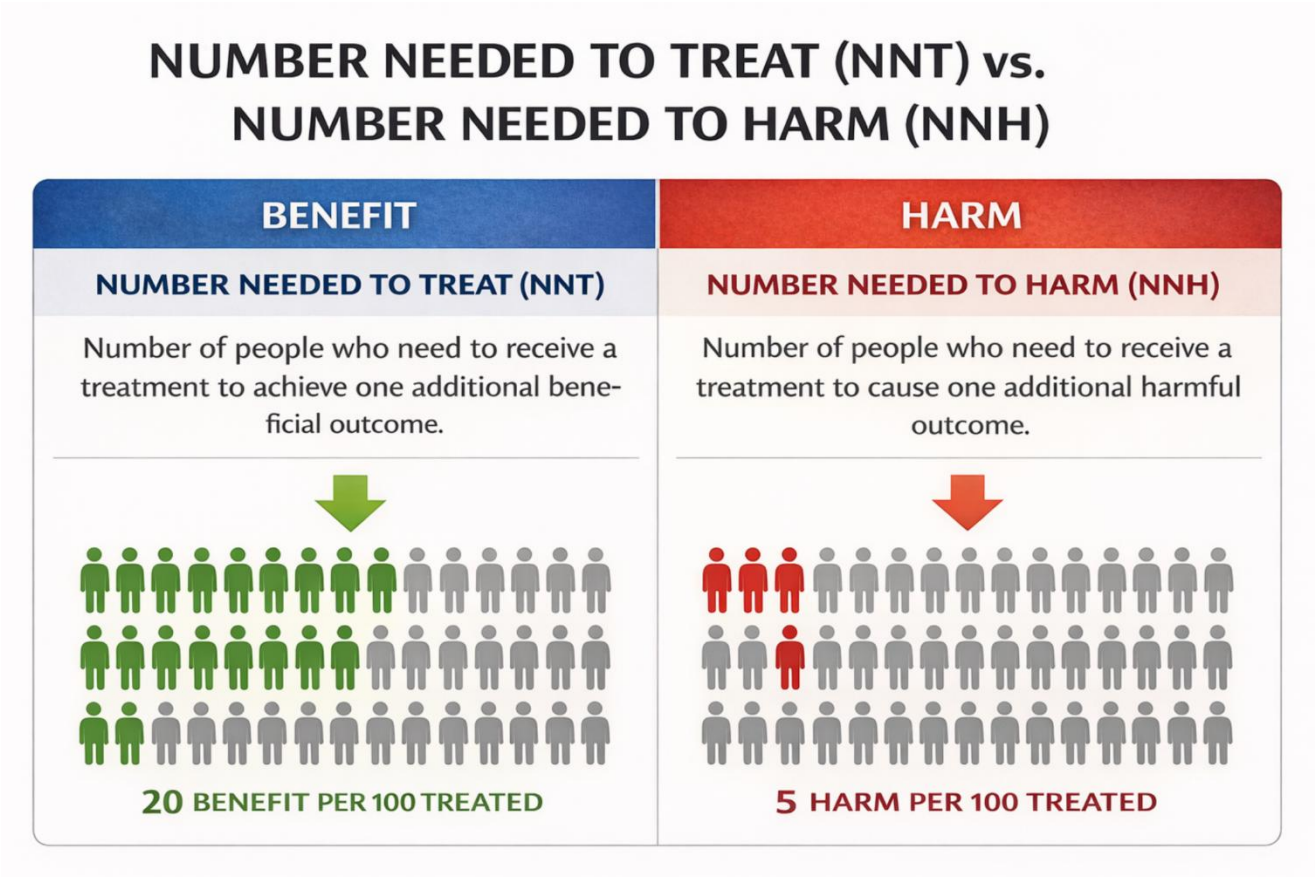


**Figure 1 Hypothetical example comparing outcome benefit versus potential harm from a treatment.**

## (iii) SEVERITY THRESHOLDS & ETHICAL CLARITY

Regulatory frameworks distinguish between:

- Grade 1–2 harms: mild, reversible, self-limiting.
- Grade 3–5 harms: severe, disabling, life-threatening, or fatal.

Informed consent must clearly differentiate between these harm categories. Prescribing thresholds must correlate with harm severity. Agents associated with Grade 3–5 risks demand heightened ethical scrutiny and explicit patient understanding of both the probability and magnitude of harm.

## (iv) THE NUTRITION BLIND SPOT

The consent framework consistently centres on pharmacological or device-based interventions, neglecting the nutritional and metabolic dimensions of illness. For chronic inflammatory, metabolic, and mood disorders, nutritional insufficiency or dysfunction may materially affect symptoms and progression.

Failure to discuss and document these dimensions narrows the patient's perception of available alternatives, undermining the ethical validity of consent.

When nutrients are automatically categorised as a medicine, based on the therapeutic action, this signals to clinicians unfamiliar with nutrients as a therapeutic that these nutrients consequently present a risk, yet the significant majority of nutrients present no more than a mild (Grade 1-2) risk at the levels recommended by practitioners. The rare nutrient that presents a higher risk are well described in the scientific literature and well known by health pracitioners.

Pharmaceutical medicines are typically developed after identifying a diagnostic or biochemical pathway associated with a disease or symptom. Drugs are designed to interrupt or suppress that pathway in order to relieve symptoms or slow disease progression.

Nutrients operate in a fundamentally different manner. Rather than targeting a single pathway, they influence interconnected physiological systems that regulate metabolism, immune activity, endocrine signalling, and cellular repair. Many nutrients exert anti-inflammatory effects and support the biological processes required for healthy cellular function.

The clinician's capacity to recognise whether a condition is primarily driven by environmental exposures, dietary patterns, or genetic predisposition plays an important role in preventing over-medication and addressing the drivers of a group of symptoms. Many clinical presentations emerge from the interaction of these factors. Addressing environmental stressors, toxic exposures, and nutrient insufficiencies therefore requires knowledge that extends beyond narrow diagnostic categories.

Conventional training rarely prepares clinicians to use nutrients therapeutically unless they are explicitly categorised as pharmaceutical agents. As a result, clinicians may not regard nutritional intervention as part of their clinical expertise.

This expertise gap has ethical implications. Before initiating pharmacotherapy, clinicians arguably have a duty to assess and correct modifiable biological constraints that influence metabolic health, neurological function, and treatment responsiveness. The ethical significance of this duty is particularly strong in populations undergoing rapid physiological development or vulnerability, including infants, children, adolescents, pregnant women, and women in the post-partum period.

### (V) HIGHER ETHICAL STANDARD FOR VULNERABLE POPULATIONS

When medicines are prescribed to young people whose neurological and endocrine systems are still developing; or during pregnancy, where maternal and foetal physiology are intertwined, the evidentiary threshold for informed consent must be higher. In practice, routine systems often lack age- and pregnancy-specific outcome transparency sufficient to meet this standard.

The central issue is not whether clinicians intend to inform patients; it is whether the system provides clinicians with the tools required to do so and whether the data is accessible to patients.

## A. CASE STUDY: REGULATION OF ANTIDEPRESSANTS

Antidepressants, including citalopram, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine may reduce suffering and restore functioning in depression, anxiety and related conditions. However, the risk to benefit value is increasingly under question. Some people experiencing no meaningful improvement, and/or a range of intolerable side effects, including suicidality.

## 1. DEVELOPMENTAL VULNERABILITY AND TREATMENT CONTEXT

Adolescence through the mid-twenties is marked by ongoing maturation of executive control networks, emotional regulation systems, and stress-response pathways. During pregnancy, immune signalling, nutrient demand, and neurodevelopmental processes are dynamic and interdependent. These physiological contexts can influence both the benefits and risks of pharmacotherapy.

Getting well involves ensuring nutrition is addressed. Untreated depression and anxiety carry real harms, including academic failure, social withdrawal, self-harm risk, and adverse pregnancy outcomes. However, adequate nutrition can support sleep, concentration, reduce fatigue and improve energy, providing resilience for the challenges of life. Ethical care therefore requires careful balancing rather than reflex avoidance or reflex prescribing.

## 2. THE NEGLECTED FOUNDATIONS OF CARE

Before initiating pharmacotherapy, clinicians have an ethical duty to assess and correct modifiable biological constraints that influence mental health and treatment response. Common insufficiencies, iron deficiency, low vitamin D, B-vitamin insufficiency, inadequate protein intake, sleep disruption, and chronic stress exposure, affect neurotransmitter synthesis, mitochondrial function, and immune regulation. Cohort and randomised control trials are now showing that multinutrient supplementation can support brain (and mental) health in a variety of ways.

Correcting deficiencies does not replace psychiatric treatment is a patient is acutely suffering. But neglecting these fundamentals can prolong illness, increase required drug doses, and reinforce a symptom-suppression model rather than restoration of health. Patients can relapse if they discontinue psychiatric medication, however doctors do not currently consider the fundamental role of nutrition in preventing and reducing many of the symptoms of psychiatric illness.

## 3. SIDE EFFECTS, TAPERING & INCOMPLETE DISCLOSURE

Youth randomised control trials (RCTs) are mostly short (weeks) and often underpowered for rare harms. Long-term RCTs are mainly in adults and focus on relapse prevention, not granular adverse-event incidence by age subgroup.

Therefore, the majority of the ‘under-25 long-term safety’ picture inevitably pulls from pooled analyses, pharmacovigilance and observational cohorts, not clean long-duration RCT incidence tables.

SSRIs and SNRIs are associated with adverse effects which can include sleep disturbance, gastrointestinal symptoms, weight loss, vomiting, emotional blunting, hyperkinesia and tremors, akathisia (severe restlessness), somnolence (drowsiness), dizziness, arrhythmia, anxiety, sexual dysfunction, and discontinuation symptoms. Evidence curves are not provided.

Early-treatment activation and suicidal ideation risk require careful monitoring.

People can experience multiple different side effects from one SSRI/SNRI. The Formulary and most datasheets do not provide efficacy or side-effect rates broken down by age and gender. Most

‘efficacy’ statements in these datasheets are not traceable to a specific named trial/publication inside the datasheet. Where named, the trials are for a short time period.

Patients rarely receive absolute risk information (for example, how many people per 100 experience specific side effects), the expected duration of adverse effects, or the likelihood and management of discontinuation symptoms. Tapering is often discussed only when problems arise rather than as part of initial consent. Tapering is ‘messy’ and low-certainty, as withdrawal is real and drug-specific, and can be mistaken for relapse.

Without absolute risk framing and taper planning, patients cannot meaningfully weigh benefit against harm. Scientists expressed concern that the published trial literature related to suicidality and aggression on antidepressants is unreliable.

### 4. TRIAL & SCIENTIFIC EVIDENCE AGE & TRANSPARENCY GAPS

In New Zealand, GPs and psychiatrists source drug information from the New Zealand Formularly, Medsafe Data Sheets (which are produced by drug companies); Many pivotal trials informing antidepressant approvals date from the 1980s through early 2000s, and this can be evidenced in international evidence syntheses, such as the Cochrane reviews.

Today’s prescribing patterns, including longer durations and wider youth use, differ from earlier contexts. Patients deserve disclosure of the age, duration, and applicability of the evidence base.

Compounding this, formularies and regulatory datasheets often summarise efficacy and safety without citing specific trials or describing study populations, gender-specific data and duration. Even though evidence may be updated, including for short and long-term safety and efficacy research, the citation and date of the study that claims the benefit or side effect is not included. This limits independent evaluation and undermines trust.

Patients and caregivers should not be required to locate and interpret foreign regulatory assessment reports or reconstruct the primary evidence base from dispersed literature in order to understand the benefit–harm profile of funded medicines. This is particularly problematic for medicines used in pregnancy and in individuals under 25 years, where clinical decision-making depends on age-, sex-, gestational-, and comorbidity-specific risk.

## B. MICRONUTRIENTS FIRST TO SUPPORT BRAIN NUTRITION

Nutrients support metabolic, immune, and neurochemical processes required for recovery and resilience, including supporting neurotransmitter signalling. Antidepressants can modify neurotransmitter signalling and downstream neuroplastic pathways. The extent to which both ‘work’ can be debated, however nutritional treatment can often address the physiology of symptoms with less severe side effects than medical drugs. These approaches are at minimum, complementary rather than competing. The ethical concern arises when pharmacologic treatment proceeds while foundational physiological needs remain unaddressed.

Under-25 brain pathways still developing. The brain doesn’t finish growing at 25, yet broad and sometimes exquisitely sensitive systemic shifts, tend to occur over certain time periods:

Ages ~10–14

- Synaptic pruning begins in earnest (selective “wiring refinement”).

- Reward/salience systems (dopaminergic circuitry) are highly reactive; emotional/novelty cues can dominate decision-making.
- Prefrontal control systems (planning, inhibition) are comparatively immature.

Ages ~15–17

- Continued pruning and network re-organisation, especially in association cortices.
- Rapid myelination improves speed/efficiency of long-range connectivity (fronto-striatal and fronto-limbic tracts).

Ages ~18–25 ('emerging adulthood')

- Prefrontal cortex maturation continues (executive control, long-term planning, impulse regulation), often cited as still developing through the early–mid 20s.
- Ongoing synaptic and myelin-related changes underpin improving 'top-down' regulation of emotion and threat responses.

**Why this matters for mental health:** during this window, circuits that regulate stress response (HPA axis), threat learning, and reward/avoidance are still calibrating. That makes sleep, nutrition, trauma exposure, and substances (including psychoactives) more consequential than in fully mature systems.

### 5. PREGNANCY: DUAL RESPONSIBILITIES OF CARE

During pregnancy, untreated depression carries risks for both mother and infant. Medication decisions should therefore include transparent discussion of maternal benefit, fetal exposure data, trimester considerations, and non-pharmacological supports — including nutrition, sleep, and psychosocial stability.

## C. HOW CURRENT REGULATIONS CONFUSE INFORMED CONSENT

Regulatory frameworks categorise substances by the threshold of harm: what the first adverse effect is, whether it is mild and reversible, whether consumers can recognise and self-manage it, and whether harm escalates unpredictably or requires monitoring.

There are structured systems used in medicine, toxicology, pharmacovigilance, and risk governance to classify severity of harm and support risk-stratified decisions. There isn't one single universal 'medical index', but several widely accepted frameworks serve this function (See Appendix below).

This logic explains why substances producing self-limiting effects (for example, gastrointestinal upset or temporary co-factor depletion) may be available for general sale, while substances with risks of serious organ toxicity, dependency, suicidality, arrhythmia, or metabolic disturbance remain prescription-only. For patients weighing nutrients versus pharmaceuticals, informed decision-making improves when risk is framed not simply as 'a risk exists', but in terms of severity, reversibility, and the need for medical oversight.

Yet this is not clear for doctors, clinicians and patients, is the likelihood of, for example, a Grade 3–5 harm (Appendix): severe, disabling, life-threatening, or fatal outcomes – by age and gender from

a psychiatric medicine, versus any equivalent risk from early-stage nutritional and dietary intervention.

But there is another problem that damages the capacity of patients to have informed consent, and it's based on how the Medicines Act 1981 works and how nutritional supplements are regulated.

Upper intake limits for nutrients are commonly based on conservative thresholds derived from early observable effects rather than severe outcomes. In many cases, the first adverse effects used to set these limits are Grade 1–2 harms: mild, reversible, and self-limiting (e.g., diarrhoea from magnesium, nausea from zinc, co-factor imbalances with high-dose single nutrients).

By contrast, Grade 3–5 harms: severe, disabling, life-threatening, or fatal outcomes, are the threshold concerns that typically justify prescription control and monitoring. This is not clear for clinicians or patients, because of the way the Medicines Act 1981 is drafted, in that it categorises nutrients as a medicine if they have a therapeutic action, rather than a grade 3-5 effect.

The problem for nutrient manufacturers who operate on slim margins, is that to become an 'off the shelf' nutrient (so-called by the legislation) 'medicine' (rather than a prescription only medicine, which is what happens when a nutrient is classified as having therapeutic potential, and therefore being categorised as a pharmaceutical medicine) they have to pay large amounts of money in fees, which is not possible for generic nutrient manufacturers.

This is a big problem that MNZH will address in another of our policies.

## 6. SIGNED CONSENT FORMS RARELY STAND UP IN COURT

A signed informed consent form does not automatically protect a clinician or institution from liability, nor does it prove that valid informed consent actually occurred.

Across the United Kingdom, Australia, and New Zealand, courts have held that a signature on a consent form provides no legal immunity where a patient was not adequately informed. Key precedents, Montgomery v Lanarkshire Health Board [2015] UKSC 11 and Rogers v Whitaker (1992) 175 CLR 479, confirm that informed consent is a process of understanding, not a paperwork exercise. In each case, the courts held that clinicians have a duty to ensure patients understand the material risks and reasonable alternatives that a person in their circumstances would consider significant.

A signed form may demonstrate that a conversation occurred, but it cannot prove that disclosure was sufficient, that risks were properly explained, or that the patient had the evidential basis to weigh alternatives.

Doctors are often expected to provide patient-centred disclosure with institutionally incomplete data. In practice, clinicians often lack access to transparent, age- and sex-specific data, absolute risk metrics, or even reliable long-term safety evidence. This information gap makes it impossible to meet the standard of 'material disclosure' defined in law. The result is an ethical and legal mismatch: health professionals are expected to deliver patient-centred consent while relying on evidence frameworks that leave both practitioner and patient inadequately informed.

This systemic deficit renders informed consent largely procedural, satisfying documentation requirements while failing the ethical and legal threshold articulated in Montgomery and Rogers:

that patients must be empowered to make decisions grounded in meaningful understanding of both benefit and harm.

## D. CAN WE 'TRUST' PHARMACEUTICAL DRUG DATA IN GENERAL?

Short-term (6-12 week) placebo controlled randomised control trials are often used to secure regulatory approval. They provide adverse event rates, efficacy endpoints, denominators and statistical comparisons. Longer-term safety information is largely derived from pharmaceutical regulatory safety datasets and surveillance, not clearly cited individual trials.:

- Extension studies (open-label continuation of RCTs)
- Maintenance/relapse-prevention trials
- Integrated safety summaries submitted to regulators
- Post-marketing pharmacovigilance
- Observational follow-up studies

These sources often lack placebo control, pool heterogeneous data, and emphasise signal detection rather than precise incidence. Regulators accept this structure because long-term placebo control is often unethical.

However, the underlying data is often not is not publicly available, nor is it disclosed to government regulators who must trust the data provided by the pharmaceutical sponsor.

Many studies (and meta-analyses) focus not on adverse event incidence but on problems with relapse, discontinuation and discontinuation. Risk and benefit.

### 7. QUALITY EVIDENCE: SYSTEMATIC REVIEWS & META-ANALYSES

Clinical decisions and policy guidance on psychiatric medicines often rest on systematic reviews and meta-analyses that appear methodologically authoritative. Yet the reliability of these syntheses depends on the integrity of the underlying trials and the assumptions built into evidence-aggregation methods. Several recurring hazards can compromise conclusions about safety and efficacy.

PRISMA is a reporting guideline designed to improve transparency. It does not ensure methodological rigour. PRISMA is not a guarantee of quality. Compliance can create a false signal of reliability if reviewer's complete checklist items without addressing deeper problems such as biased study selection, inappropriate pooling, or missing data. Reporting completeness does not equal low risk of bias, and peer review rarely audits adherence in detail. When PRISMA is applied late, as a submission checklist rather than a design framework, it cannot correct flawed decisions made upstream.

Publication and reporting biases distort the evidence base. Trials with favourable results are more likely to be published, cited, and included in reviews. Negative or null findings may remain unpublished or be reframed through outcome switching or selective reporting. Meta-analyses built on the published literature therefore risk overstating benefit and understating harm. Adjustments for publication bias frequently shrink effect sizes, indicating systematic inflation.

Industry funding and conflicts of interest shape design and interpretation. Industry-sponsored trials are statistically more likely to report favourable outcomes. Influence may occur through comparator choice, dosing strategies, outcome selection, analytic decisions, or selective dissemination. Disclosure alone does not eliminate these structural incentives.

Design features can exaggerate benefit and obscure harms. Common issues include short trial durations that limit long-term safety inference; enriched run-in periods that exclude early non-responders or those experiencing adverse effects; exclusion of complex or high-risk patients, reducing real-world applicability; and side-effect-induced unblinding, which can bias subjective outcomes. Withdrawal effects may be misclassified as relapse in discontinuation studies.

Quantification and pooling problems complicate interpretation. Meta-analyses often combine heterogeneous populations, interventions, and outcome measures into a single pooled effect that may not apply to any real patient group. Standardised mean differences can appear statistically significant while masking modest clinical benefit. Absolute risk reduction and harm rates are frequently underreported, impeding informed consent and risk communication.

Meta-analyses can perpetuate flawed data. When biased primary studies dominate the evidence base, meta-analysis can amplify rather than correct distortion. Narrow outcome framing may privilege symptom-scale changes while overlooking functional outcomes, quality of life, or adverse effects.

In sum, transparency tools improve reporting but do not resolve structural vulnerabilities in psychiatric drug evidence. Policymakers and clinicians should interpret pooled findings cautiously, prioritise access to full trial data, insist on absolute risk reporting, and scrutinise conflicts of interest and external validity before drawing conclusions about safety and efficacy.

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## APPENDIX [1] GRADING ADVERSE EVENTS

Systems used in medicine, toxicology, pharmacovigilance, and risk governance to classify severity of harm and support risk-stratified decisions

### 1. Standard adverse-event severity grading (clinical & regulatory)

**CTCAE — Common Terminology Criteria for Adverse Events**

Used in clinical trials and pharmacovigilance worldwide.

| Grade | Severity | Meaning | Example |
|---|---|---|---|
| **Grade 1** | Mild | transient, no treatment needed | mild nausea, headache |
| **Grade 2** | Moderate | minimal intervention | persistent GI upset |
| **Grade 3** | Severe | medically significant | dehydration needing IV fluids |
| **Grade 4** | Life-threatening | urgent intervention | cardiac arrhythmia |
| **Grade 5** | Death | fatal | — |

**Use:** risk–benefit assessment, regulatory decisions, safety labelling.

## 2. WHO adverse drug reaction (ADR) seriousness criteria

Used globally in pharmacovigilance.

An adverse event is "serious" if it results in:

- ✓ death
- ✓ life-threatening event
- ✓ hospitalisation
- ✓ disability/incapacity
- ✓ congenital anomaly
- ✓ medically important event

Everything else is *non-serious*. This matters, as regulators often focus on whether risks are serious, not merely whether they exist.

## 3. Toxicology severity tiers (risk assessment & poisoning medicine)

Often expressed as:

**Minor:** Transient symptoms, no medical treatment needed

Examples: mild GI upset, headache

**Moderate:** Systemic symptoms requiring treatment

Examples: persistent vomiting, electrolyte imbalance

**Severe:** Organ injury or life-threatening physiology

Examples: renal failure, seizures, cardiac arrhythmia

**Fatal:** Death

Used in poison control and chemical safety risk assessment.

## 4. Risk matrix frameworks (public health & regulation)

Risk = **severity × likelihood**

Severity tiers often include:

- Negligible
- Minor
- Moderate
- Major
- Catastrophic

**Likelihood tiers:**

- Rare
- Unlikely
- Possible
- Likely
- Almost certain

This approach is widely used in environmental health and regulatory governance.

## 5. Nutrient & exposure risk frameworks (relevant to trace elements)

Regulators typically distinguish:

**Mild / reversible effects**

- transient GI upset
- minor metabolic disturbance

**Functional impairment**

- altered nutrient status
- endocrine disruption

**Structural or organ damage**

- bone changes
- thyroid disease
- renal injury

**Life-threatening toxicity**

This is the logic behind Upper Limits (ULs): they are usually set to prevent the first clear adverse effect, not catastrophic toxicity.

## 6. Example continuum (plain language)

**Minimal / nuisance**

- transient nausea if taken without food
- mild headache

**Mild but clinically relevant**

- persistent GI upset
- reversible electrolyte disturbance

**Moderate harm**

- thyroid dysfunction
- sustained blood pressure changes

**Serious harm**

- kidney injury
- cardiac arrhythmia
- neurological toxicity

**Critical harm**

- organ failure
- life-threatening electrolyte disturbance

## APPENDIX [2] THE ETHICAL FOUNDATIONS OF INFORMED CONSENT

Informed consent rests upon a set of ethical principles that guide clinical decision-making and protect the dignity, welfare, and rights of patients. These principles: autonomy, non-maleficence, beneficence, and justice, form the core ethical architecture of modern clinical medicine and public health. They help ensure that clinical authority is exercised responsibly and that patients are able to make voluntary and informed decisions regarding their care.

**Autonomy.** Autonomy is commonly regarded as the overarching principle in clinical ethics because it protects the individual's right to make informed and voluntary decisions about their own health and life. Autonomy requires that individuals be able to deliberate and act free from coercion, undue influence, manipulation, or misinformation. Gillon has described autonomy as deliberated self-rule.

> *'the ability and tendency to think for oneself, to make decisions for oneself about the way one wishes to lead one's life based on that thinking, and then to enact those decisions.'*[1]

Autonomy refers to deliberated self-rule: the capacity to reflect, to evaluate information, and to choose a course of action consistent with one's own values and judgement.[2] In the clinical setting, respecting autonomy requires that patients receive information that is sufficiently accurate, transparent, and comprehensible to enable meaningful participation in decisions about diagnosis, treatment, and prevention. Respect for autonomy therefore places a moral constraint on both paternalistic clinical beneficence and broader institutional forms of paternalism within health systems.[1] [2]

[1] Gillon R. Ethics needs principles—four can encompass the rest—and respect for autonomy should be "first among equals." J Med Ethics 2003;29:307–312.
[2] Gigerenzer G, Gaissmaier W, Kurz-Milcke E, Schwartz LM, Woloshin S. Helping doctors and patients make sense of health statistics. Psychological Science in the Public Interest. 2007;8(2):53-96.

**Non-maleficence.** The principle of non-maleficence has its origins in the Hippocratic maxim *primum non nocere*, 'first, do no harm'. It requires clinicians and health systems to avoid causing unnecessary injury or suffering through acts of commission or omission. In practice, this principle obliges health professionals to carefully evaluate the potential harms associated with medical interventions, including adverse drug effects, treatment burdens, and the unintended consequences of medical decision-making.

Non-maleficence is particularly important in modern clinical practice, where increasingly complex interventions and polypharmacy can introduce new risks. Ethical medical practice therefore requires a continuous assessment of whether the harms associated with treatment may outweigh the benefits.

**Beneficence.** Beneficence refers to the moral obligation to act in ways that promote the welfare of patients and protect their legitimate interests. It encompasses actions that prevent harm, remove existing harms, and contribute positively to the health and wellbeing of others.[4]

Unlike non-maleficence, which establishes a clear duty to avoid harm, beneficence is often described as an imperfect obligation. It requires professional judgement to determine when and how intervention is appropriate, and how competing interests should be balanced. Clinical beneficence therefore requires clinicians to consider the full range of interventions available, including medical, environmental, nutritional, and behavioural strategies, that may reduce suffering and improve long-term health outcomes. [3] [4]

**Justice.** The principle of justice concerns fairness in the distribution of health resources, risks, and outcomes. Justice requires that individuals have equitable opportunities to achieve and maintain health, and that health systems avoid perpetuating avoidable inequalities.

However, justice is not satisfied by treating all individuals identically. Ethical approaches to justice therefore recognise that equitable outcomes may require proportionate responses to differing levels of disadvantage in proportion to their degree of need.[5]

> *'Accounting for human heterogeneity is important: justice requires aiding people in proportion to their degree of disadvantage, according to Aristotle's proportionality principle. Additionally, health capability determinants vary across societies, and assessing health capability inequalities must account for these differences.'* [6]

Justice demands equal opportunities, however there is an important nuance, as justice demands the fair distribution of health outcomes, or health equity (as opposed to exclusively focusing on equity of medical treatment.[7]

Together, these four principles provide the ethical foundation for informed consent. They require that clinicians provide patients with transparent, accurate, and contextually relevant information,

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[3] Beauchamp, Tom, "The Principle of Beneficence in Applied Ethics", The Stanford Encyclopedia of Philosophy (Spring 2019 Edition), Edward N. Zalta (ed.), https://plato.stanford.edu/archives/spr2019/entries/principle-beneficence.
[4] Gillon R. Ethics needs principles—four can encompass the rest.
[5] Ruger JP. Good medical ethics, justice and provincial globalism. Journal of Medical Ethics. 2015;41:103–106.
[6] Schröder-Bäck P. et al (2014). Teaching seven principles for public health ethics: towards a curriculum for a short course on ethics in public health programmes. BMC Med Ethics. 15:73. http://www.biomedcentral.com/1472-6939/15/73
[7] Ruger JP. Good medical ethics, justice and provincial globalism. J Med Ethics 41:103-106. http://dx.doi.org/10.1136/medethics-2014-102356

enabling individuals to make decisions that reflect both their values and their understanding of potential benefits and harms.