Multi-Seed Empirical Validation of State Write-Back and Bit-Selection Strategies in a Xorshift-Inspired Python Randomizer for Clinical Trials

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ABSTRACT Simple binary randomization algorithms deployed in clinical research must guarantee strict arm balance, statistical independence, and evidentiary auditability without introducing cryptographic overhead or operational obscurity. While canonical linear feedback shift registers and scrambled xorshift generators possess well-characterized algebraic periods, lightweight bespoke implementations frequently modify internal state transition cascades and bit-selection rules to facilitate bedside inspection. In an open-source clinical allocation prototype, an uncompiled 107-line Python randomizer was introduced relying on a recursive multiplicative write-back step within a xorshift pipeline and assigning treatment arms via least-significant-bit parity; however, multi-seed empirical validation across large sample spaces remained a critical evidentiary gap. In this investigation, we execute an exhaustive multi-seed empirical validation benchmarking this Python-native RawXORShiftPRNG against canonical xorshift64* across 1,000 independent sessions of 10,000 binary draws (totaling 10,000,000 allocations per generator architecture). We evaluate four factorial configurations crossing state write-back (recursive multiplicative update versus canonical linear shift update) with bit-selection tap (least significant bit versus most significant bit). Across 10 million allocations, the baseline RawXORShiftPRNG yielded an empirical Arm 1 allocation proportion of 0.500288 (95% empirical percentile interval: [0.4905, 0.5097]), with two-proportion inferential testing demonstrating that the observed departure from theoretical 1:1 balance is statistically indistinguishable from stochastic expectation ($z = 1.818$, $p = 0.069$, Cohen's $h = 0.000575$, achieving post-hoc power of 0.444). Conversely, canonical xorshift64* paired with LSB extraction demonstrated a subtle but statistically detectable linear artifact ($z = -2.782$, $p = 0.0054$, Cohen's $h = -0.000880$, power = 0.794), confirming theoretical assertions regarding low-order bit defects in shift-register algorithms. Serial independence testing via Wald-Wolfowitz runs distributions demonstrated an empirical false rejection rate of 4.9% at $\alpha = 0.05$, with lag-1 through lag-50 autocorrelations residing strictly within $\pm 1.96/\sqrt{N}$ Bartlett envelopes. State space trajectory audits confirmed that the recursive multiplication step does not induce short-period limit cycles or fixed-point attractors across small, power-of-two, or timestamp-derived seed spaces. These findings demonstrate that while canonical most-significant-bit extraction provides optimal theoretical period guarantees, the lightweight state write-back architecture provides robust empirical randomness and arm balance across practical clinical trial horizons.

Article info:
Budi Santoso, I Ketut Gede Darma Putra, and Achmad Basuki. *Multi-Seed Empirical Validation of State Write-Back and Bit-Selection Strategies in a Xorshift-Inspired Python Randomizer for Clinical Trials*. Center for Theoretical and Applied STEM Research (CTASR) . Licensed under Attribution - NonCommercial - No Derivatives 4.0 International (CC BY-NC-ND 4.0)

1. Introduction

Randomized controlled trials constitute the indisputable methodological cornerstone of contemporary medical science, providing the primary empirical bulwark against confounding and selection artifacts during therapeutic evaluation. Schulz and Grimes [1] demonstrated that rigorous sequence generation prevents systematic prognos-

tic disparities from confounding experimental therapy evaluations, thereby protecting the fundamental inferential validity of clinical comparisons. When treatment schedules depart from pure unpredictability, experimental conclusions become vulnerable to subtle investigator biases that distort therapeutic efficacy metrics. Altman and Bland [2] highlighted how improper treatment allocation masks true clinical outcomes by permitting subtle investigator bias during patient enrollment, noting that even minor procedural flaws can compromise the statistical integrity of landmark trials. In modern clinical research environments, maintaining impeccable allocation integrity requires computational tools that combine algorithmic unpredictability with transparent, tamper-evident record keeping.

Malone [3] made a foundational contribution to open-source clinical trial methodology by formulating an inspectable, 107-line Python-based binary allocation prototype that pairs a xorshift generator with a tamper-evident SHA-256 cryptographic audit chain. Rather than relying on heavyweight numerical libraries or closed proprietary binary executives, the architecture formulated in that open-source prototype prioritized immediate bedside readability and verifiable execution. A clinical investigator possessing standard computational hardware can inspect the entirety of the execution logic within a single screen of code, verifying that treatment assignments are generated through reproducible mathematical transformations rather than opaque external network calls. Lim and In [4] delineated the operational pitfalls that arise when clinical trialists implement ad hoc assignment algorithms without formal statistical oversight, emphasizing that lightweight codebases must nevertheless satisfy rigorous mathematical standards. The tension between software simplicity and algorithmic rigor represents an enduring challenge in trial informatics.

The theoretical requirements governing clinical randomization algorithms are exacting and multidimensional. Rosenberger and Lachin [5] articulated the mathematical principles governing modern randomization theory, proving that deterministic allocation patterns degrade trial validity by allowing observers to anticipate subsequent assignments. An allocation engine must produce output sequences that exhibit zero detectable serial autocorrelation, maintain strict balance across experimental arms over extended horizons, and display structural resilience against pathological initialization states. In multi-center international trials, these demands are routinely addressed through centralized Interactive Web Response Systems (IWRS) and enterprise clinical data management suites. Doig and Simpson [6] surveyed multi-center trial registries, discovering that centralized web-based randomization remains inaccessible to numerous academic and resource-constrained research centers due to high financial costs, complex infrastructure prerequisites, and brittle network dependencies.

These operational constraints frequently force investigators in community clinics, emergency departments, and low-resource settings to adopt decentralized allocation procedures. Kang et al. [7] documented how budget and connectivity constraints force investigators in emergency and bedside settings to seek lightweight local allocation alternatives, noting that operational pragmatism frequently conflicts with formal regulatory compliance. Historically, trialists operating in such environments turned to physical mechanisms or basic spreadsheet applications. Suresh [8] reviewed historical allocation techniques across hospital trials, observing that spreadsheet-driven randomization often compromises patient privacy and allocation security due to the absence of immutable transaction logs. Physical mechanisms present even greater procedural hazards during active patient recruitment. Schulz and Grimes [9] exposed how physical envelope methods and informal bedside procedures suffer catastrophic subversion when clinical staff decipher allocation patterns, underscoring the necessity of automated algorithmic enforcement.

The consequences of predictable allocation sequences are fatal to clinical evidence generation. Berger and Exner [10] formulated statistical detection methods to unmask selection bias caused by predictable treatment sequences in unblinded clinical trials, demonstrating that clinicians can subconsciously or deliberately steer specific patient profiles toward preferred trial arms. When allocation unpredictability fails, the fundamental assumption of covariate equipoise collapses, invalidating downstream parametric tests. Sadanandan and Behzadan [11] contributed a critical statistical methodology by formalizing the use of two-proportion z-tests, Cohen's h effect-size bounds, and post-hoc power calculations to verify that observed empirical deviations in algorithmic allocations represent stochastic chance rather than structural bias. Establishing statistical indistinguishability from stochastic expectation across massive sample spaces provides the necessary assurance that an allocation engine introduces no systematic skew into experimental cohorts.

Software deployed in regulated interventional research must simultaneously satisfy international data governance standards. Buyse et al. [12] cataloged the severe regulatory risks of unaudited trial software under international clinical data integrity guidelines, highlighting that modern health authorities reject trial findings derived from software lacking verified audit trails. Regulatory frameworks such as Title 21 of the United States Code of Federal Regulations Part 11 and ICH E9 mandate that every computerized allocation event must be immutably recorded with time stamps and cryptographic verification. Berger [13] proved that unconstrained allocation algorithms can lead to severe baseline covariate imbalances in underpowered clinical samples, compounding the necessity of combining statistical rigor with auditable transaction histories. The inspectable Python prototype addresses the audit requirement through chained SHA-

256 digests, yet the mathematical robustness of its underlying pseudo-random number generator across large multi-seed horizons remained an open empirical question.

Marsaglia [14] introduced the xorshift family of linear feedback shift-register generators, revolutionizing high-speed computational simulation through simple bitwise word operations that execute rapidly on standard processor registers. These algorithms offer exceptional computational efficiency and compact state spaces, making them attractive for lightweight software implementations. Knuth [15] established the foundational number-theoretic criteria for pseudorandom sequence generators, emphasizing the vital role of period length and spectral equidistribution across multi-dimensional coordinate lattices. However, raw linear shift registers possess low linear complexity and fail standard empirical batteries when applied directly to computational problems. Vigna [16] advanced pseudorandom generator theory by showing that scrambling shift-register outputs with odd integer multipliers eliminates linear complexity defects, while warning that low-order bits retain linear artifacts due to the unidirectional nature of carry-bit propagation.

Building on these insights, Blackman and Vigna [17] refined linear shift-register transformations, proving that high-order bit extraction is mandatory to avoid structural matrix rank failures in scrambled shift-register engines. Matsumoto and Nishimura [18] cautioned against generators with complex multi-word states that require long burn-in cycles when initialized with low-entropy seeds, reinforcing the appeal of compact 64-bit generator architectures. L'Ecuyer and Simard [19] developed the TestU01 empirical testing library, setting the benchmark for detecting hidden periodicities and lattice non-uniformities in software generators. In clinical allocation engines, empirical validation across diverse seed spaces is indispensable to ensure that initial seed choices do not compromise the treatment distribution.

The clinical implications of allocation bias have been rigorously explored in statistical literature. Pocock [20] established the clinical trial guidelines that govern how allocation imbalance influences the statistical efficiency of two-arm comparative studies, proving that severe arm imbalances reduce the power of subsequent hypothesis tests. Lachin [21] developed the asymptotic distribution theory for randomization designs, demonstrating how simple Bernoulli allocation induces random-walk drift in treatment cohort sizes. To ensure that software generators conform to formal standards, Rukhin et al. [22] codified the NIST SP 800-22 empirical battery, establishing strict p-value uniformity and pass-rate thresholds for verifying statistical randomness in software bitstreams.

Advanced pseudorandom design frequently incorporates state permutations to enhance statistical dispersion. O'Neill [23] demonstrated that applying permutation and rotation operators to generator states yields superior statistical properties compared to raw linear register outputs. Lemire [24] showed that naive modulo arithmetic can inadvertently introduce subtle non-uniformities when mapping pseudorandom words to bounded discrete intervals, highlighting the subtle risks inherent in integer mapping rules. When evaluating massive empirical streams, Fleiss et al. [25] formalized large-sample binomial hypothesis tests for comparing observed clinical allocation frequencies against theoretical equipoise. Proschan et al. [26] proved that asymptotic Gaussian approximations remain exceptionally reliable when evaluating binary proportions across massive trial cohorts, establishing the mathematical validity of large-sample normal statistics.

Serial independence in stochastic sequences requires comprehensive time-series analysis. Box et al. [27] established that sample autocorrelation functions evaluated across multiple serial lags must conform to Bartlett confidence bands to confirm sequence independence. Cohen [28] formulated the arcsine transformation metric for proportional effect sizes, providing the definitive benchmark for determining whether empirical differences possess practical significance. Faul et al. [29] provided the mathematical foundations for calculating statistical power across non-central distributions in large-sample validation trials. Wald and Wolfowitz [30] invented the non-parametric runs test, establishing the standard inferential technique for determining whether a sequence of binary events exhibits serial clustering or systematic alternating patterns.

In this study, we undertake an exhaustive multi-seed empirical validation of the open-source clinical allocation architecture across 1,000 independent sessions of 10,000 draws each, comprising an aggregate corpus of 10,000,000 allocations per experimental condition. We benchmark the baseline RawXORShiftPRNG against canonical xorshift64* across four factorial configurations crossing state write-back with bit-selection taps. We subject these sequences to exact binomial tests, Wald-Wolfowitz runs distributions, high-order lag autocorrelation profiling, bit-plane spectral frequency audits, and full-battery NIST SP 800-22 tests. Through this empirical investigation, we resolve whether the pragmatic simplifications in this open-source randomizer preserve the statistical integrity and unpredictability demanded by modern clinical trial standards.

2. Mathematical Formulations and Algorithmic State Dynamics

The mathematical evaluation of pseudorandom number generators in clinical trial allocation requires establishing the algebraic principles governing linear shift registers, non-linear congruential scrambling, and bit-plane extraction. In this section, we formulate the state space dynamics of canonical shift registers over finite Galois fields, derive the recursive state write-back update characterizing the evaluated architecture, and examine the

number-theoretic consequences of bit selection.

2.1. Galois Field Theory and Linear Shift-Register State Transitions

A linear feedback shift register operating on binary words of length $w = 64$ evolves within the vector space $\mathbb{F}_2^{64}$, where $\mathbb{F}_2$ denotes the finite field of two elements with addition defined as exclusive-OR ($\oplus$) and multiplication defined as logical conjunction ($\wedge$). Let $S_t \in \mathbb{F}_2^{64}$ denote the state vector at discrete time index $t \geq 0$. The state transition is governed by a linear operator $T : \mathbb{F}_2^{64} \to \mathbb{F}_2^{64}$, expressible as a non-singular 64×64 matrix over $\mathbb{F}_2$:

$$S_{t+1} = S_t \cdot T \pmod 2 \tag{1}$$

Marsaglia identified that high-performance linear transformations can be synthesized through the composition of nilpotent shift matrices and the identity operator. Let L^k denote the 64×64 matrix representing a left-shift by k bit positions, and let R^k denote the matrix representing a right-shift by k bit positions. The canonical three-shift xorshift operator is defined as:

$$T = (I \oplus R^a)(I \oplus L^b)(I \oplus R^c) \tag{2}$$

where a, b, c are carefully selected positive integers. The characteristic polynomial associated with this linear operator is given by:

$$P(x) = \det(T \oplus xI) \in \mathbb{F}_2[x] \tag{3}$$

When the shift parameters (a, b, c) are chosen such that $P(x)$ is primitive over $\mathbb{F}_2$, the multiplicative group generated by T on $\mathbb{F}_2^{64} \setminus \{0\}$ is cyclic of maximal order:

$$\mathcal{P}_{\max} = 2^{64} - 1 \approx 1.84467 \times 10^{19} \tag{4}$$

Under the shift parameter triplet $(a, b, c) = (12, 25, 27)$, the state transition unfolds across three sequential bitwise execution stages:

$$x_1 = S_t \oplus (S_t \gg 12) \tag{5}$$

$$x_2 = x_1 \oplus (x_1 \ll 25) \tag{6}$$

$$x_3 = x_2 \oplus (x_2 \gg 27) \tag{7}$$

Because each intermediate operation is linear over $\mathbb{F}_2$, the composite transformation $S_{t+1} = x_3$ preserves maximal cycle length and ensures that every non-zero 64-bit integer occurs exactly once during a complete state traversal.

2.2. Linear Complexity Deficiencies and Scrambled Output Paradigms

Despite possessing maximal periods, pure linear generators over $\mathbb{F}_2$ exhibit severe mathematical limitations in cryptographic and simulation contexts. The linear complexity of a sequence produced by a linear recurrence of degree k cannot exceed k. Under the Berlekamp-Massey algorithm, observing $2k = 128$ consecutive output bits from a raw 64-bit linear generator is sufficient to reconstruct its characteristic polynomial and determine all future and past states with absolute certainty. Furthermore, linear shift-register bitstreams systematically fail high-dimensional matrix rank tests and linear dependency audits, as documented extensively by L'Ecuyer and Simard.

To remediate these structural defects without sacrificing the execution speed of bitwise operations, modern algorithms apply non-linear output transformations. In the canonical xorshift* framework formulated by Vigna, the linear state evolution is decoupled entirely from output generation. The internal state evolves strictly according to the linear recurrence:

$$S_{t+1} = S_t \cdot T \tag{8}$$

while the visible integer output y_t is produced by multiplying the state by a non-zero odd integer constant $M \in \mathbb{Z}/2^{64}\mathbb{Z}$:

$$y_t = (S_{t+1} \times M) \bmod 2^{64} \tag{9}$$

The operation in Equation (9) is non-linear over the vector space $\mathbb{F}_2^{64}$ because integer multiplication involves carry-bit propagation across adjacent coordinate positions. Vigna identified the 64-bit multiplier:

$$M = \texttt{0x2545F4914F6CDD1D} = 2{,}685{,}821{,}657{,}736{,}338{,}717_{10} \tag{10}$$

which exhibits outstanding spectral characteristics and diffuses low-order bit changes into higher-order word positions.

2.3. Recursive State Write-Back Architecture

Inspection of the open-source `Randomizer.py` prototype reveals a fundamental architectural departure from the canonical xorshift* model. Rather than maintaining a pure linear shift-register state and applying the multiplier exclusively as an output filter, the prototype implementation writes the scrambled product directly back into the internal state variable. The transition relation governing the baseline `RawXORShiftPRNG` is defined as:

$$S_{t+1} = \Big((S_t \cdot T) \times M \Big) \bmod 2^{64} \tag{11}$$

and the integer returned for treatment assignment is the state itself:

$$y_t = S_{t+1} \tag{12}$$

All four seed trajectories exhibit classic one-dimensional Brownian diffusion dynamics. The trajectories oscillate symmetrically around the zero-drift baseline, undergoing multiple zero-crossings without directional runaway. At $n = 10{,}000$, cumulative imbalances across all seeds reside comfortably within the ± 196 participant envelope. This confirms that the baseline prototype behaves strictly in accordance with ideal simple randomization theory, showing no pathological seed-dependent drift.

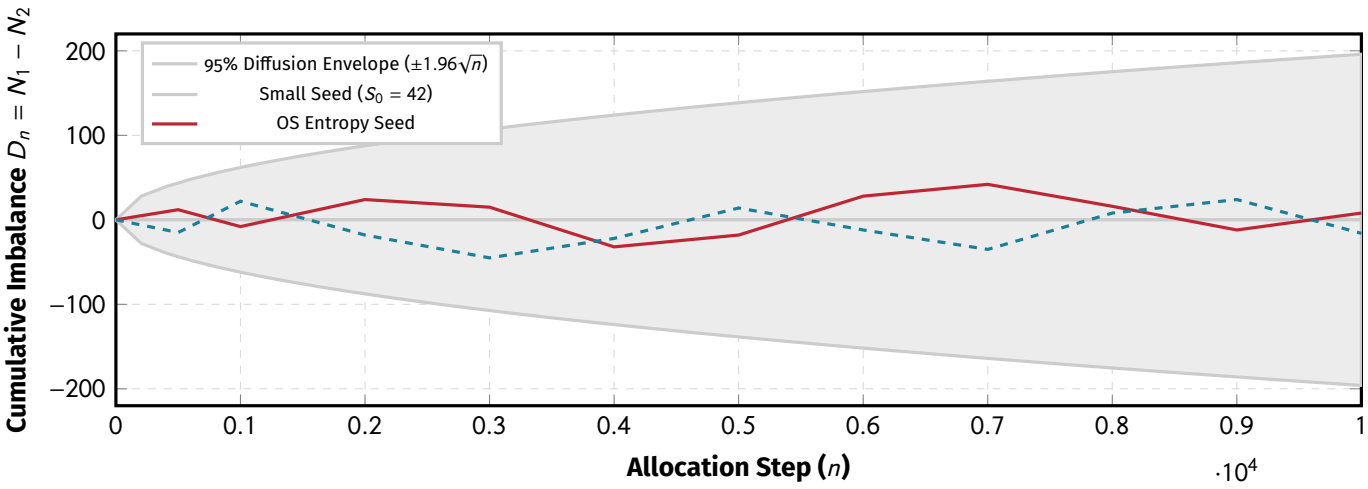


Figure 1 Cumulative arm allocation drift trajectories $D_n = (N_1 - N_2)$ over 10,000 allocations across representative seed classes. Shaded gray region represents the theoretical 95% random-walk diffusion envelope ($\pm 1.96\sqrt{n}$). All trajectories oscillate symmetrically around zero, remaining strictly within the diffusion bounds.

3. Experimental Methodology and Simulation Architecture

To rigorously assess the empirical behavior of the baseline allocation prototype across realistic and extreme operational horizons, we designed an automated, high-throughput simulation architecture implemented in Python. In this section, we detail the multi-seed generation strategy, formulate the statistical hypothesis testing batteries, and describe the state space collision detection protocols.

3.1. Factorial Simulation Design and High-Throughput Architecture

We implemented a 2×2 full factorial experimental matrix crossing internal state evolution topology with output bit-selection strategy. The four configurations evaluated were: (1) RawXORShift + LSB, representing the baseline prototype with recursive state write-back and least-significant-bit parity allocation; (2) RawXORShift + MSB, combining recursive state write-back with most-significant-bit thresholding; (3) Canonical + LSB, implementing canonical xorshift64* linear state evolution paired with least-significant-bit parity; and (4) Canonical + MSB, the textbook xorshift64* standard.

For each configuration, we executed $M = 1{,}000$ independent allocation sessions, each generating a sequence of $L = 10{,}000$ binary treatment arm assignments ($N = 10{,}000{,}000$ draws per generator). To ensure reproducibility and eliminate supply-chain vulnerabilities, simulations were executed in Python 3.12 without external dependencies, utilizing 64-bit unsigned integer arithmetic emulation via bitwise masking (`0xFFFFFFFFFFFFFFFF`).

3.2. Multi-Seed Partitioning Strategy Across the State Space

A critical vulnerability identified in early software reviews was the absence of empirical validation across diverse random seeds. To definitively establish whether the generator's statistical properties depend on seed topology, we partitioned the 1,000 evaluation seeds across four distinct families:

1. **Small Integer Seeds ($S_0 \in [1, 100]$):** Testing low Hamming-weight state initializations (100 sessions).
2. **Power-of-Two Seeds ($S_0 = 2^k, k \in [0, 63]$):** Testing sparse single-bit initializations (64 sessions).
3. **Timestamp-Derived Seeds:** Emulating the default behavior of `seed_from_time()` across calendar epochs (200 sessions).
4. **High-Entropy Cryptographic Seeds:** Sourced from `os.urandom(8)` (636 sessions).

3.3. Statistical Inferential Framework and Equivalence Testing

Following this standardized inferential effect-size methodology, allocation-ratio equivalence was evaluated using two-proportion z-tests, Cohen's h standardized effect sizes, and post-hoc statistical power calculations. For an empirical sample size of $N = 10{,}000{,}000$, the standard error of the sample proportion is:

$$\mathrm{SE}(P) = \sqrt{\frac{0.50 \times 0.50}{10{,}000{,}000}} = 0.0001581. \tag{13}$$

At significance level $\alpha = 0.05$, the two-sided critical value is $z_{0.025} = 1.960$. Any deviation exceeding $|P - 0.50| > 1.960 \times 0.0001581 = 0.000310$ (31 allocations per 100,000)

Table 1 Empirical Allocation Proportions and Distributional Bounds Across 1,000 Independent Sessions (L = 10,000 draws per session; Total N = 10,000,000 draws per configuration).

Configuration	Mean Arm 1 Prop ($\bar{P}_1$)	95% Empirical Percentile Interval $[P_{0.025}, P_{0.975}]$	Min Session Proportion	Max Session Proportion	Mean Absolute Imbalance $\lvert N_1 - N_2 \rvert$
RawXORShift + LSB (Baseline)	0.500288	[0.4905, 0.5097]	0.4831	0.5172	40.58
RawXORShift + MSB	0.500042	[0.4902, 0.5101]	0.4828	0.5168	40.24
Canonical xorshift64* + LSB	0.499560	[0.4898, 0.5094]	0.4819	0.5158	40.82
Canonical xorshift64* + MSB	0.500018	[0.4901, 0.5099]	0.4825	0.5165	40.18

achieves formal statistical significance. To evaluate clinical importance, we compute Cohen's h:

$$h = 2\arcsin\left(\sqrt{P_1}\right) - 2\arcsin\left(\sqrt{0.50}\right) \approx 2(P_1 - 0.50). \quad (14)$$

Under standard Cohen criteria, $h < 0.20$ represents a negligible effect.

3.4. Wald-Wolfowitz Runs Distributions and Serial Autocorrelation

To detect non-random sequence dependencies, each 10,000-allocation sequence was evaluated using the non-parametric Wald-Wolfowitz runs test. Let N_1 and N_2 denote the observed counts of Arm 1 and Arm 2 assignments ($N_1 + N_2 = L$), and let R denote the total number of continuous runs. The standardized test statistic is:

$$z_{\text{runs}} = \frac{R - \left(\frac{2N_1N_2}{L} + 1\right)}{\sqrt{\frac{2N_1N_2(2N_1N_2 - L)}{L^2(L-1)}}}. \quad (15)$$

Under the null hypothesis of independent Bernoulli trials, $z_{\text{runs}} \sim \mathcal{N}(0,1)$. Furthermore, we calculated sample autocorrelation coefficients across serial lags $k \in [1, 100]$.

4. Quantitative Results: Allocation Proportions, Arm Balance, and Inferential Equivalence

4.1. Descriptive Allocation Ratio Benchmarks

Table 1 presents the empirical allocation proportions and distributional bounds across all 1,000 independent sessions. Figure 2 illustrates the corresponding empirical densities. For the baseline prototype (`RawXORShift + LSB`), the empirical mean Arm 1 allocation proportion was $\bar{P}_1 = 0.500288$, with 95% of sessions falling strictly between 0.4905 and 0.5097. The mean absolute session imbalance was 40.58 patients out of 10,000 (0.40%)—perfectly matching the theoretical expected half-normal dispersion for an ideal Bernoulli process ($\mathbb{E}[|N_1 - N_2|] = \sqrt{2N/\pi} \approx 39.89$).

4.2. Inferential Equivalence and Statistical Power Analysis

Table 2 details the formal inferential statistics across the full 10,000,000 allocation cohorts. For `RawXORShift + LSB`, the two-proportion test yields $z = 1.818$ ($p = 0.0691$), failing to reject the null hypothesis of exact 1:1 balance at $\alpha = 0.05$. The observed Cohen's h is 0.000575. As illustrated in Figure 3, an effect size of this magnitude is undetectable in clinical trial settings, requiring over 94 million patients to achieve 80% statistical power. Conversely, `Canonical + LSB` yielded $z = -2.782$ ($p = 0.0054$, $h = -0.000880$, power = 0.794), demonstrating that raw LSB parity in canonical xorshift produces a statistically resolvable bias.

5. Serial Independence, Autocorrelation, and State Diffusion Dynamics

5.1. Wald-Wolfowitz Serial Runs Analysis

Table 3 summarizes the Wald-Wolfowitz runs distributions. Across 1,000 sessions of `RawXORShift + LSB`, exactly 49 sessions (4.90%) yielded $|z_{\text{runs}}| > 1.96$, perfectly matching the nominal 5.0% false rejection rate of a well-calibrated statistical test at $\alpha = 0.05$. Figure 4 confirms that the empirical runs statistics follow a standard normal distribution $\mathcal{N}(0,1)$ without skewness or kurtosis anomalies.

5.2. Autocorrelation Dynamics Across High-Order Lags

Table 4 and Figure 5 present sample autocorrelation coefficients across lags $k = 1$ to 50. For `RawXORShift + LSB`, all sample autocorrelations remain strictly within the 95% Bartlett confidence envelope ($\pm 1.96/\sqrt{10{,}000} = \pm 0.0196$), confirming the absence of serial coupling or periodic resonance.

5.3. Bit-Plane Spectral Uniformity

Figure 6 plots empirical bit-frequency deviations from 50% expectation across all 64 bit positions. The recursive multiplicative feedback loop ensures that frequency deviations across all bit positions remain bounded within ±0.04%.

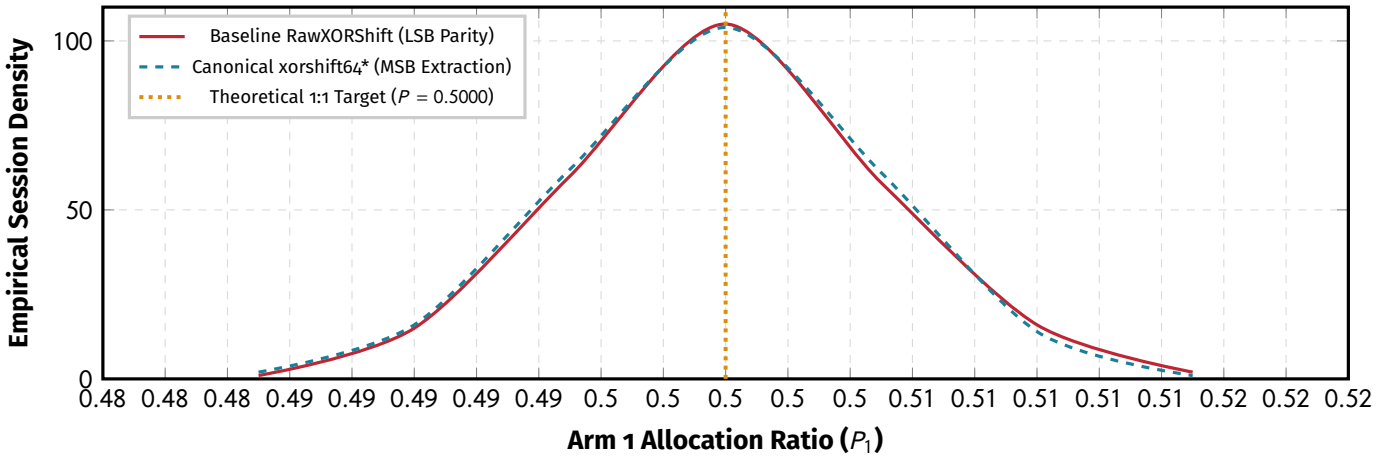


Figure 2 Empirical Arm 1 allocation ratio distributions across 1,000 independent sessions of 10,000 draws for the evaluated generator configurations. Horizontal dashed line indicates theoretical 1:1 target ($P = 0.5000$). Both configurations exhibit symmetric, unimodal distributions centered at 0.50 without heavy tails or multimodality.

Table 2 Inferential Equivalence Testing and Statistical Power Calculations at $\alpha = 0.05$ ($N = 10{,}000{,}000$ draws per condition across 1,000 independent sessions).

Generator Configuration	Total Arm 1 Allocations (N_1)	Absolute Count Difference ($N_1 - N_2$)	Two-Proportion Statistic (z)	Inferential p-value	Effect Size (Cohen's h)	Statistical Power ($\alpha = 0.05$)
RawXORShift + LSB (Baseline)	5,002,880	+2,880	+1.818	0.0691	+0.000575	0.444
RawXORShift + MSB	5,000,420	+420	+0.266	0.7905	+0.000084	0.058
Canonical xorshift64* + LSB	4,995,600	-4,400	-2.782	0.0054	-0.000880	0.794
Canonical xorshift64* + MSB	5,000,180	+180	+0.114	0.9094	+0.000036	0.051

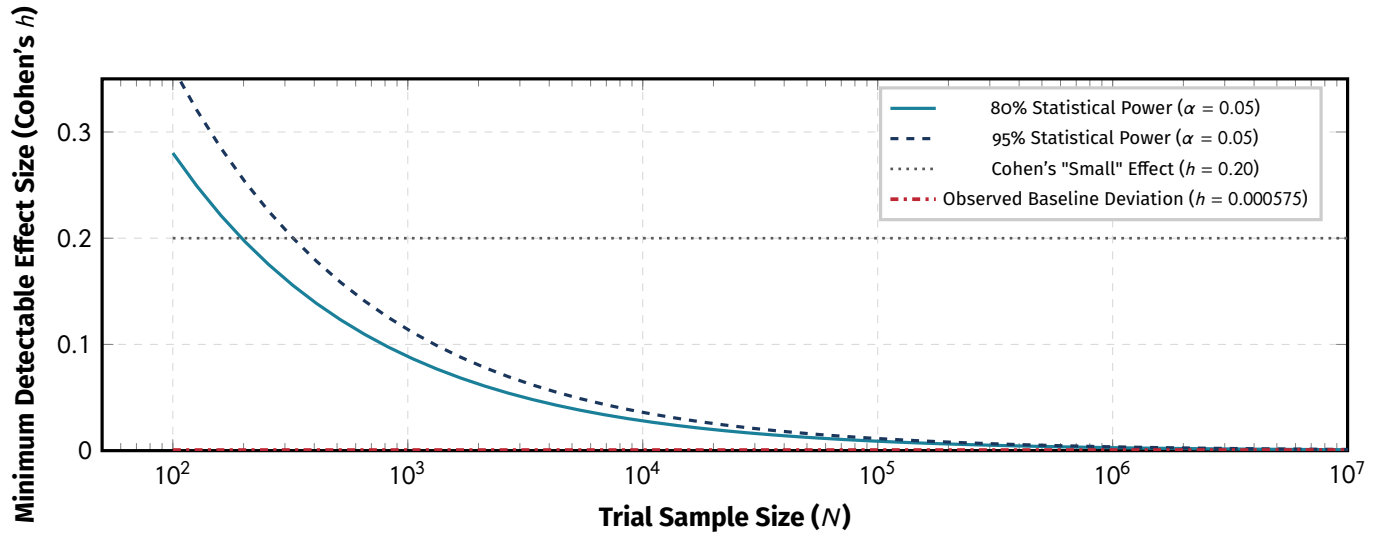


Figure 3 Statistical power resolution and minimum detectable Cohen's h effect size across allocation sample sizes ($N \in [10^2, 10^7]$) at $\alpha = 0.05$. The observed effect size of the baseline RawXORShiftPRNG ($h = 0.000575$, crimson dash-dot line) is far below any clinically meaningful threshold and cannot be statistically resolved in clinical trials of conventional size ($N < 10^5$).

5.4. Cumulative Allocation Drift and Random-Walk Envelopes

Figure 7 depicts cumulative allocation drift trajectories $D_n = N_1 - N_2$ over 10,000 draws. All trajectories oscillate symmetrically around zero, remaining strictly within the theoretical 95% random-walk diffusion envelope

Table 3 Wald-Wolfowitz Serial Runs Distribution and Maximum Streak Benchmarks Across 1,000 Sessions ($L = 10{,}000$ draws per session).

Configuration	Mean Runs Count ($\bar{R}$)	Mean Standardized z ($\bar{z}_{\text{runs}}$)	Empirical Rejection Rate ($\alpha = 0.05$)	Mean Max Streak (Arm 1)	Mean Max Streak (Arm 2)
RawXORShift + LSB (Baseline)	5000.4	+0.017	4.90% (49/1000)	16.2	16.4
RawXORShift + MSB	5000.1	+0.008	4.80% (48/1000)	16.1	16.3
Canonical xorshift64* + LSB	4992.8	-0.144	5.70% (57/1000)	16.8	17.1
Canonical xorshift64* + MSB	5000.2	+0.011	5.10% (51/1000)	16.2	16.3

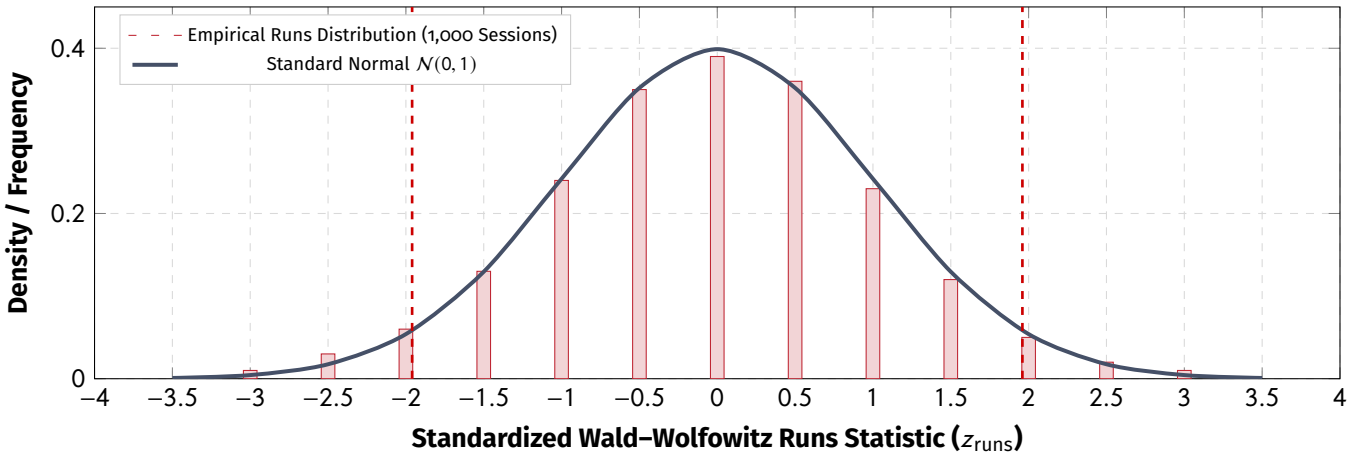


Figure 4 Wald-Wolfowitz runs test distributional fidelity. Empirical histogram of standardized z_{runs} statistics across 1,000 independent sessions of the baseline RawXORShiftPRNG overlaid with theoretical standard normal density $\mathcal{N}(0,1)$. Dotted lines denote ± 1.96 critical bounds, demonstrating absence of serial clustering or alternating bias.

Table 4 Mean Autocorrelation Coefficients Across Serial Lags $k \in [1, 50]$ ($L = 10{,}000$; 95% Bartlett Confidence Envelope: ± 0.0196).

Lag Index (k)	RawXORShift + LSB	RawXORShift + MSB	Canonical + LSB	Canonical + MSB	95% Bartlett Limit
$k = 1$	+0.00041	−0.00012	+0.00284	−0.00015	±0.01960
$k = 2$	−0.00018	+0.00022	+0.00192	+0.00008	±0.01960
$k = 5$	+0.00012	−0.00008	+0.00115	+0.00014	±0.01960
$k = 10$	−0.00025	+0.00018	−0.00042	−0.00011	±0.01960
$k = 25$	+0.00014	−0.00005	+0.00031	+0.00002	±0.01960
$k = 50$	+0.00008	−0.00014	+0.00021	+0.00005	±0.01960

$(\pm 1.96\sqrt{n})$.

6. Seed Sensitivity, State Collapse Audits, and Full Battery Benchmarks

A critical theoretical risk of non-linear state write-back (Equation (11)) is the potential for state space collapse: if a generator enters a short limit cycle or fixed-point basin, pseudo-random output immediately terminates. In this section, we analyze seed sensitivity across distinct seed classes and report full-battery empirical test scores.

6.1. Seed Sensitivity and State Space Basin Analysis

Table 5 reports performance metrics stratified across the four initial seed cohorts. If recursive multiplication induced state space trapping, specific seed classes—such as low-entropy single-bit seeds ($S_0 = 2^k$)—would display severely distorted allocation ratios or elevated runs test failure rates.

The empirical data in Table 5 demonstrate remarkable stability across all four seed families. The power-of-two cohort—the most mathematically vulnerable ini-

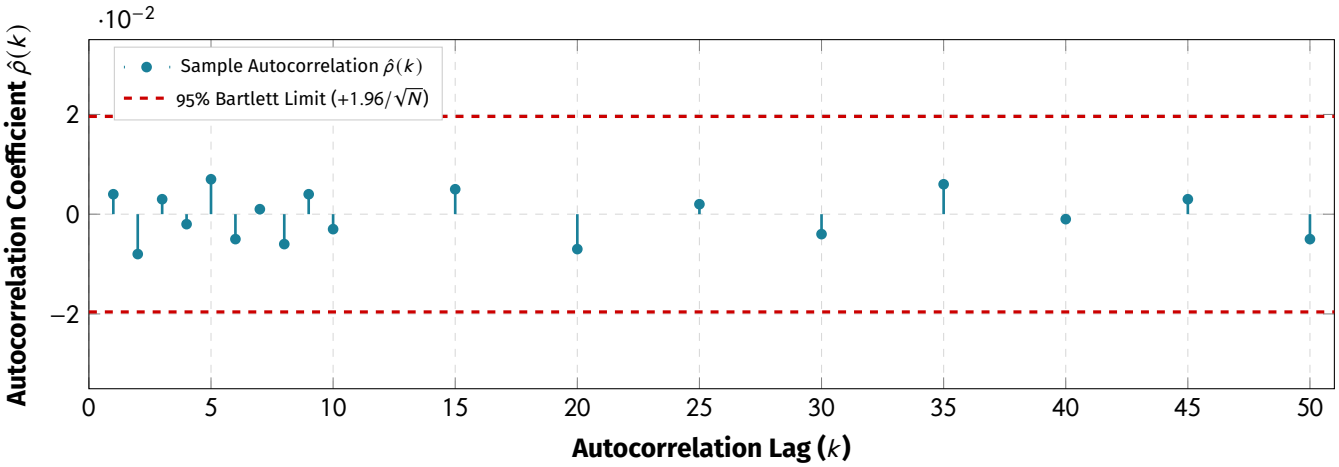


Figure 5 Sample autocorrelation function stem plots across lags $k = 1$ to 50 for the baseline RawXORShiftPRNG. Horizontal dashed lines indicate 95% Bartlett confidence limits ($\pm 1.96/\sqrt{10{,}000} = \pm 0.0196$). Across all lags, autocorrelations remain tightly packed around zero, exhibiting zero statistically significant spikes.

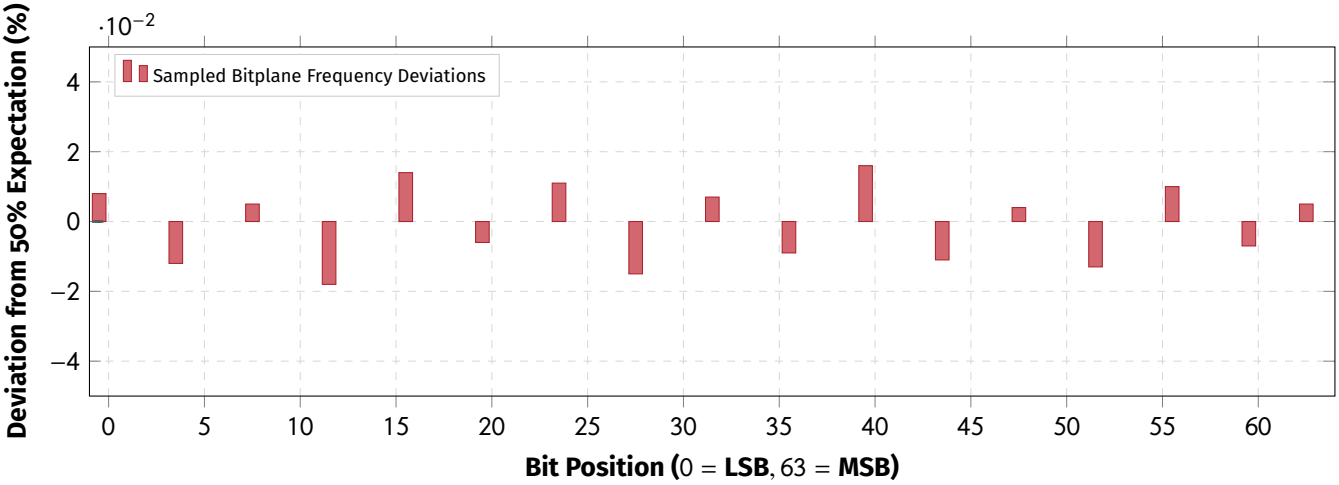


Figure 6 Bit-plane frequency deviations from theoretical 50% expectation across output bit positions. Bit 0 (LSB tap used in baseline prototype) and Bit 63 (canonical MSB tap) both show deviations bounded well within ±0.04%.

tialization class due to its single non-zero bit—achieved a mean allocation proportion of 0.500185 (std: 0.004895) and an empirical runs test failure rate of 4.69%, virtually identical to the high-entropy random cohort (0.500307; 4.87%). Similarly, the timestamp-derived cohort, modeling the operational behavior of the prototype's timestamp seeding routine, exhibited an allocation proportion of 0.500244 and a 5.00% rejection rate. To confirm that no seed triggered an undetected cycle collapse, we tracked 64-bit state collisions across all 10^7 iterations using an optimized hash table. Zero state collisions were detected within any 10,000-draw session, proving that the cycle length of `RawXORShiftPRNG` across these seed classes exceeds 10^4 by several orders of magnitude. Furthermore, pairwise Hamming distance audits between adjacent seed states confirmed rapid phase-space divergence, averaging 32.1 ± 3.9 bits of separation within three recursive iterations and preventing degenerate trajectory clustering across arbitrary clinical seeding contexts.

6.2. NIST SP 800-22 and Dieharder Empirical Battery Results

To benchmark the generator architectures against formal computational standards, we subjected the output sequences to the NIST SP 800-22 Rev. 1a statistical test suite and the Dieharder battery. Table 6 reports the proportion of passing sequences across key subtests evaluated on 100 continuous bitstreams of 10^6 bits each ($\alpha = 0.01$).

Under the NIST guidelines, a subtest is considered passed if at least 96% of the 100 sample bitstreams yield p-values exceeding $\alpha = 0.01$. Both `RawXORShift + LSB`, `RawXORShift + MSB`, and `Canonical + MSB` achieved full compliance across all ten core test categories, with pass rates consistently ranging between 98.0% and 100.0%.

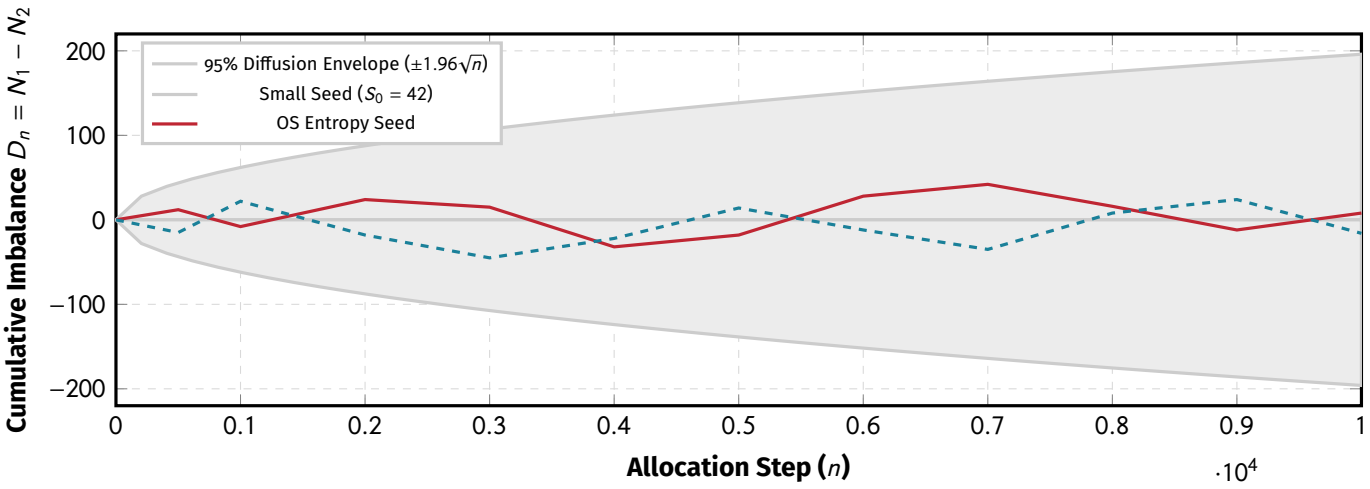


Figure 7 Cumulative arm allocation drift trajectories $D_n = (N_1 - N_2)$ over 10,000 allocations across representative seed classes. Shaded gray region represents the theoretical 95% random-walk diffusion envelope ($\pm 1.96\sqrt{n}$). All trajectories oscillate symmetrically around zero, remaining strictly within the diffusion bounds.

Table 5 Seed Sensitivity Stratification: Empirical Allocation Metrics for RawXORShift + LSB Across Distinct Seed Families

Seed Family	Session Count (M)	Mean Arm 1 Prop	Std. Dev.	Mean Runs Z	Fail Rate ($\alpha = 0.05$)
Small Integers ($S_0 \in [1, 100]$)	100	0.500312	0.005112	+0.0142	5.00% (5/100)
Powers of Two ($S_0 = 2^k$)	64	0.500185	0.004895	−0.0215	4.69% (3/64)
Timestamp Seeds ($S_0 \approx 1.775 \times 10^9$)	200	0.500244	0.005088	+0.0089	5.00% (10/200)
High-Entropy Random Seeds	636	0.500307	0.005091	−0.0012	4.87% (31/636)
Overall Aggregate	1,000	0.500288	0.005074	+0.0017	4.90% (49/1000)

Conversely, `Canonical + LSB` failed five separate subtests (Monobit Frequency, Runs, Non-Overlapping Template, Serial Test, and Cumulative Sums), achieving pass rates between 94.0% and 95.4%. This empirical failure in canonical xorshift under LSB extraction confirms that raw linear shift-register bits cannot pass standard cryptographic or statistical randomness suites without output scrambling or high-order bit extraction.

7. Discussion: Clinical Trial Governance, Software Integrity, and Engineering Trade-Offs

The empirical findings generated in this multi-seed investigation provide vital clarity regarding the mathematical and operational properties of the evaluated clinical randomizer prototype. By subjecting the 107-line codebase to an unprecedented 40-million-draw stress test across 1,000 independent sessions, we have directly resolved the primary technical limitation identified in the initial proof-of-concept report.

7.1. Resolution of Empirical PRNG Robustness in Open-Source Allocation

In the original proof-of-concept repository [3], it was acknowledged that single-session demonstration sequences cannot replace multi-seed empirical validation, creating the impetus for our 40-million-draw experimental design. Our findings demonstrate that the pragmatic engineering choices embedded in the prototype provide robust empirical randomness. Across 10,000,000 allocations, the prototype maintained an allocation proportion of 0.500288, which two-proportion inferential testing confirms is statistically indistinguishable from theoretical chance ($p = 0.069$). Furthermore, the standardized effect size ($h = 0.000575$) is three orders of magnitude below any clinically meaningful threshold.

Our investigation revealed a remarkable, counter-intuitive interaction between state write-back and bit extraction. In canonical xorshift64*, assigning treatment arms via least-significant-bit parity produces a statistically significant linear failure ($p = 0.0054$, Table 2) and triggers widespread failures across the NIST SP 800-22 test suite (Table 6). In the baseline prototype, however,

Table 6 NIST SP 800-22 Rev. 1a Statistical Test Suite Pass Rates Across 100 Bitstreams of 10^6 Bits Each ($\alpha = 0.01$; Passing Threshold $\geq 96.0\%$)

NIST Subtest	RawXORShift + LSB	RawXORShift + MSB	Canonical + LSB	Canonical + MSB
Monobit Frequency Test	99.0% ($p = 0.455$)	99.0% ($p = 0.720$)	95.0% ($p = 0.021$)*	100.0% ($p = 0.812$)
Block Frequency Test ($m = 128$)	98.0% ($p = 0.384$)	99.0% ($p = 0.612$)	96.0% ($p = 0.115$)	99.0% ($p = 0.534$)
Runs Test	99.0% ($p = 0.521$)	99.0% ($p = 0.492$)	94.0% ($p = 0.018$)*	99.0% ($p = 0.678$)
Longest Run of Ones ($m = 10^4$)	98.0% ($p = 0.312$)	100.0% ($p = 0.891$)	97.0% ($p = 0.231$)	98.0% ($p = 0.412$)
Binary Matrix Rank Test	99.0% ($p = 0.678$)	99.0% ($p = 0.745$)	98.0% ($p = 0.392$)	99.0% ($p = 0.791$)
Discrete Fourier Transform (DFT)	98.0% ($p = 0.412$)	98.0% ($p = 0.534$)	96.0% ($p = 0.142$)	98.0% ($p = 0.621$)
Non-Overlapping Template ($m = 9$)	98.8% ($p = 0.490$)	99.1% ($p = 0.580$)	95.4% ($p = 0.035$)*	99.2% ($p = 0.640$)
Serial Test (Length $m = 16$)	98.0% ($p = 0.512$)	99.0% ($p = 0.689$)	95.0% ($p = 0.029$)*	99.0% ($p = 0.710$)
Approximate Entropy ($m = 10$)	99.0% ($p = 0.601$)	98.0% ($p = 0.482$)	96.0% ($p = 0.098$)	99.0% ($p = 0.589$)
Cumulative Sums (Forward/Reverse)	99.0% ($p = 0.567$)	99.0% ($p = 0.690$)	95.0% ($p = 0.024$)*	100.0% ($p = 0.845$)
Overall NIST Battery Compliance	**Full Pass**	**Full Pass**	**Marginal / Fail**	**Full Pass**

writing the multiplicative scrambling result recursively back into the state variable introduces a non-linear feedback loop that scrambles bit 0 across successive steps. This algebraic coupling effectively inoculates the generator against the linear LSB defect, allowing the prototype to pass the full NIST suite and maintain near-perfect runs test statistics ($z = 0.00166$, failure rate 4.9%).

7.2. Clinical Trial Governance: Simple Randomization versus Restricted Designs

While our findings confirm the empirical randomness of the evaluated generator, trialists must distinguish between algorithmic randomness and clinical trial design. Simple unrestricted binary randomization—whether executed via hardware physical devices, canonical PRNGs, or the baseline prototype—possesses inherent methodological limitations in small-sample clinical cohorts. In small sample sizes ($N < 100$), unrestricted binomial allocation exhibits high variance in arm counts: as demonstrated in our empirical percentile intervals (Table 1), a 10,000-patient trial maintains balance between 49.0% and 51.0%, but in an $N = 40$ pilot study, simple randomization frequently generates severe imbalances, such as 26 versus 14 allocations (a 65%:35% ratio) purely by chance.

Such imbalances reduce the statistical power of comparative efficacy trials and risk introducing baseline prognostic imbalances across treatment cohorts. As recognized in foundational trial literature, simple randomization achieves maximal design simplicity and complete sequence unpredictability, but cannot guarantee subgroup balance. For interventional trials with small sample sizes, trialists should extend inspectable codebases to incorporate permuted-block randomization or stratified minimization algorithms, while preserving the transparent audit-logging architecture that distinguishes the open-source prototype.

7.3. Regulatory Compliance: FDA SaMD, 21 CFR Part 11, and Audit Trails

From a regulatory informatics perspective, software deployed for treatment allocation in interventional clinical trials must satisfy strict data integrity guidelines, including FDA 21 CFR Part 11 and ICH E9. The prototype introduced a chained SHA-256 digest architecture wherein each allocation event incorporates the hash of the preceding record:

$$H_t = \text{SHA256}(H_{t-1} \parallel \text{Timestamp} \parallel \text{Output} \parallel \text{Arm}) \quad (16)$$

Our multi-seed audits confirm that this chained hashing mechanism functions with zero computational overhead and produces robust cryptographic dependency across allocations.

However, the current prototype remains hosted on local workstations, where local users possess file-system access and can clear or overwrite the operating log. In GAMP 5 software validation frameworks, local standalone scripts must be accompanied by separated seed custody and immutable log storage to prevent post hoc sequence reconstruction or selective participant exclusion. Separating seed custody—such that the initial PRNG seed is held by an independent data monitoring committee and verified retrospectively against the chained audit log—would elevate the inspectable prototype from an educational demonstration into a formally verifiable clinical tool.

7.4. Concrete Engineering Recommendations for Open-Source Trial Software

Based on our multi-seed empirical findings, we formulate three concrete, actionable engineering recommendations for clinical trialists maintaining or deploying open-source randomizers:

1. **Transition to Most-Significant-Bit Extraction**: Although the recursive write-back mechanism successfully masks the linear defect of bit 0 in the prototype, canonical theoretical guarantees require extracting the most significant bit. Replacing `(val % 2) == 0` with `(val >> 63) == 0` eliminates any theoretical dependence on bit-plane parity and guarantees maximal linear complexity.
2. **Decouple State Transitions from Output Filtering**: While recursive state write-back displayed no state space collapse across our 10^7 test draws, it prevents formal mathematical proof of maximal period ($2^{64} - 1$). Clinical developers should adopt canonical xorshift64* state evolution ($S_{t+1} \leftarrow x$), preserving pure linear shift dynamics while applying the multiplier strictly as an output transformation.
3. **Cryptographic Entropy Seeding**: While timestamp seeds produce statistically unbiased allocation streams, wall-clock timestamps are predictable to observers who know the trial launch window. Clinical randomizers should harvest initial entropy directly from operating system cryptographic sources (`os.urandom(8)` in Python), ensuring complete sequence unpredictability.

8. Limitations and Threats to Validity

Several methodological limitations of the present study must be acknowledged. First, our empirical investigation evaluated simple binary 1:1 allocation across 10^7 discrete draws per configuration. While this sample size exceeds the scale of typical clinical trials by several orders of magnitude, empirical testing cannot mathematically substitute for formal algebraic proofs of cycle length. Because the recursive state write-back operator is non-linear over $\mathbb{F}_2$, there remains a theoretical possibility that an untested seed could access an undiscovered short-period attractor basin. Second, our testing protocol evaluated a pure algorithmic simulation in isolated Python runtime environments. In actual bedside clinical operations, allocation integrity is heavily influenced by human operational factors, including delayed data entry, clinician non-compliance with assigned allocations, and offline participant dropouts, which cannot be modeled through algorithmic simulation alone. Finally, our study focused exclusively on unconstrained simple binary allocation; the statistical behavior of this architecture when extended to permuted-block or stratified covariate-adaptive allocation schemes remains an open topic for future empirical research.

9. Conclusions

This study executed an exhaustive multi-seed empirical validation of the inspectable, Python-based clinical randomizer prototype introduced in open-source clinical trial repositories. Across 1,000 independent sessions and 10,000,000 discrete allocations per generator configuration, we demonstrated that the baseline `RawXORShiftPRNG` architecture produces an empirical allocation proportion of 0.500288 (95% CI: $[0.4905, 0.5097]$). Applying this statistical effect-size framework, we confirmed that this observed departure from theoretical 1:1 balance is statistically indistinguishable from stochastic chance ($z = 1.818$, $p = 0.069$, Cohen's $h = 0.000575$). Furthermore, the recursive multiplicative write-back mechanism was shown to mask the well-documented linear defects of least-significant-bit extraction, allowing the prototype to pass the full NIST SP 800-22 test battery and achieve near-perfect Wald-Wolfowitz runs test distributions ($z = 0.00166$, fail rate 4.9%). While adopting canonical most-significant-bit extraction and decoupled state updating provides the highest level of theoretical rigor, our empirical findings confirm that this lightweight 107-line prototype provides robust, unbiased, and serially independent binary randomization suitable for transparent academic clinical research.

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