Using AI/ML and human review to empirically measure intentional dose non-adherence: impact on clinical trial methodology and data interpretation

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1 – Introduction

- While the accurate estimation of intentional non-adherence (INA) rates in clinical trials is essential to determining the dose-response relationship, no accurate estimates have ever been produced. Several articles have characterized efforts by study volunteers to conceal non-adherence but there has never been a direct empirical measure of this behavior.
- This study used a platform combining artificial intelligence and human review to quantify the scope of these behaviors in 23 CNS trials conducted between December 2016 and May 2019.

Methodological questions being addressed

- New technologies that can identify and quantify the scope of intentional non-adherence in clinical trials have the potential to improve data quality by ensuring more precise measurement of true treatment effects.

2 – Methodology

- A dataset containing 257,672 anonymized dosing administration results of study volunteers taking their clinical trials medications, across 23 trials, from 2,796 participants were analyzed. All participants were based in the United States.
- Dosing administrations were classified by the platform as INA based on a combination of AI and human review. Chi-square was used to test for significant differences between means.
- A logistic regression model was run on data from 19 clinical trials — those containing complete data — to investigate the relationship between characteristics of clinical trial design and intentional dose non-adherence.

Data Characteristics

	Doses Observed	Study Volunteers Observed	Clinical Trials Observed
Total	257,672	2,976	23
By Phase			
1	409	10	1
2a	157,508	1,084	14
2b/3	89,314	1,521	7
4	10,441	361	1
By Disease Condition			
Schizophrenia	82,831	502	7
Addiction	80,436	644	2
Adult ADHD	61,305	500	3
Manic Depressive Disorder	14,115	462	4
Health Volunteers	10,850	370	2
Urinary Tract Infection	6,113	442	1
Epilepsy	932	8	1
Bipolar Depression	432	34	1
Parkinson's Disease	351	3	1
Post Traumatic Stress	307	13	1

Overall Adherence Rates

	Total Observed Doses (N=257,672)	Percent of Total Observed Doses
Confirmed Adherent Doses	189,749	73.6%
Confirmed Intentionally Non-Adherent Doses	8,022	3.1%
Unable to Confirm	59,901	23.3%

Clinical Trial Characteristics Predictive of INA

Variable		Odds ratio (95% CI)	P-Value
Disease Condition			
	Healthy Volunteers	1 (Referent)	
	Addiction	.163 (.043 - .626)	<.01
	Adult ADHD	.611 (.315 – 1.18)	.144
	Bipolar Depression Disorder	4.05 (1.13 – 14.6)	<.05
	MDD	.960 (.643 – 1.43)	.843
	PTSD	.192 (.055 - .666)	<.01
	Schizophrenia	.170 (.058 - .498)	<.01
	UTI	2.91 (1.16 – 7.32)	<.05
Clinical Trial Phase			
	Phase 2	1 (Referent)	
	Phase 1	.144 (.030 - .701)	<.05
	Phase 3	1.28 (.819 – 2.01)	.276
Region where Clinical Trial Took Place			
	West	1 (Referent)	
	Midwest	.525 (.380 - .724)	<.001
	Northeast	1.26 (.943 – 1.67)	.119
	Southeast	1.20 (.970 – 1.49)	.093
	Southwest	.775 (.585 – 1.03)	.077
Investigative Site Enrollment Volume		.995 (.991 - .999)	<.05
Clinical Trial Duration		1.39 (1.19 – 1.63)	<.001
Number of Pills taken Concomitantly			
	1	1 (Referent)	
	2	.578 (.298 – 1.12)	.105
	3	.828 (.594 – 1.15)	.264
	4	N/A	N/A
	5	.470 (.253 - .875)	<.05

3 – Results

- Of the total 2,976 study volunteers evaluated, 48.0% had at least one INA dose; 6.0% had 10%-20% of their total doses INA; 2.8% had between 20% and 30% of their doses INA; one-out-of-twenty study volunteers (4.8%) were intentionally non-adherent for >30% of their total doses (N=142).
- Several factors were associated with INA doses, including:
  - Treatment duration (p<.001)
  - Participants whose first dose in the clinical trial was intentionally non-adherent (p<.001)
  - Participants with at least one INA dose in the first week of the clinical trial (p<.001).
  - Site geography. Sites in the Western United States, North East and South East had higher relative INA rates (p<.001).

4 – Conclusion

- To our knowledge, this study was the first to obtain data from dosing administrations confirmed to be intentionally non-adherent based on a combination of human review and AI.
- From this sample, 3.1% of all observed doses were intentionally non-adherent; nearly 1 in ten (9%) of all study volunteers had over 10% of their total doses identified as intentionally non-adherent.
- Several factors were associated with, and predictive of, intentional non-adherence.
- The ability to measure and mitigate intentional non-adherence impacts several methodological areas, including:
  - Enrichment strategies: exclusion criteria based on pre-specified thresholds of intentional non-adherence during a placebo lead-in period and/or post-randomization;
  - More precise estimation of sample size;
  - Enhanced interpretation of placebo response based on differentiating dose non-adherence from intentional dose non-adherence.

Intentional Non-Adherence by Disease Condition

Disease Condition	Percent of Total Doses that were Intentionally Non-Adherent (N=257,672)	Percent of Patients with 10% or More Intentionally Non-Adherent Doses
Urinary Tract Infection	9.3%	23.5%
Bipolar Disorder	6.5%	26.5%
Manic Depression	5.5%	16.7%
Healthy Volunteers	4.7%	15.9%
Addiction	3.5%	8.5%
Schizophrenia	2.6%	13.0%
PTSD	2.6%	38.5%
Adult ADHD	1.8%	6.0%
Epilepsy	1.3%	11.1%
Parkinson's Disease	0.3%	0.0%
Overall Average	3.1%	13.6%

Distribution of Participants with INA Doses

	Participants	Percent of Total
	(N=2,976)	
Intentionally non-adherent for 10% or fewer total doses	1,024	34.4%
Intentionally non-adherent for >10% but <20% of total doses	180	6.0%
Intentionally non-adherent for >20% but <30% of total doses	83	2.8%
Intentionally non-adherent for greater than 30% of total doses	142	4.8%

Overall INA Rate per Patient based on INA Rate During the First Week of the Clinical Trial

First Week Status	(n)	Intentional Non-Adherence Rate	CoV	F-value	P-value
1st Third of Trial				1502.6	<.001
≥1 Alert	743	19.8% (1.11)	1.11		
No Alert	2,134	0.8% (3.49)	3.49		
2nd Third of Trial				318.3	<.001
≥1 Alert	619	14.1% (2.56)	2.56		
No Alert	1,696	1.9 (3.41)	3.41		
3rd Third of Trial				99.1	<.001
≥1 Alert	493	9.7% (2.49)	2.49		
No Alert	1,419	2.3% (3.62)	3.62		