International Journal of Reliable and Quality E-Healthcare
Volume 11 • Issue 1

Probability of Medication Adherence When Alarm Is Used as a Reminder

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ABSTRACT

The main objective of this research is to find the effect of alarm as a form of reminder in improving medication adherence rate. Medication non-adherence is a problem that adversely impacts patients' health, finances, and longevity. Several factors are associated with medication non-adherence. This research uses the method of probability estimates, risk difference, relative risk, and odds ratio to analyze the probability of an increase in medication adherence among patients who use the alarm as a form of reminder. By clustered sampling and a structured questionnaire, 525 responses were obtained from patients suffering from different types of diseases in the state of Sikkim, India. It has been observed that using the alarm as a form of reminder significantly improves adherence rates. The odds of not missing a dose reduces to 49.3%. At a personal level, the chance of not missing the dose reduces by 32.6%, and if the total population is considered, 16.4% of people will not skip the dose if a reminder in the form of an alarm is used.

KEYWORDS

Adherence, Alarm, Medication Adherence, Medication Regime, Patient Beliefs, Reminder, Weight Gain

INTRODUCTION

Medication non-adherence is a common problem. Patients discontinue their prescribed medication due to several factors. It is estimated that nearly 50% of patients fail to take their medications as prescribed (WHO, 2015). The disadvantages of medication non-adherence are many. It is related to

DOI: 10.4018/IJRQEH.305221 *Corresponding Author

reduced clinical benefits, enhanced costs and morbidity (Eliasson et al., 2020). Medication adherence is complex, and to overcome the problem, several barriers must be addressed (Pandey et al., 2020; Saha et al., 2022b). There is no "gold-standard method" to accurately measure adherence (Poulter et al., 2019). Several techniques are used to measure adherence: direct observation, pill count, self-reporting etc. (Al-Ganmi et al., 2020). Several researchers have used ratio analysis to study the effect of interventions on diseases (Foroutan et al., 2020; Saha et al., 2021c, 2021a). A study using the ratio analysis technique found that exposure to pets and farm animals helped reduce acute lymphoblastic leukemia risk among children (Figueroa et al., 2020). However, the literature suggests a lack of reports related to long term studies and appropriate statistical analysis (Liu & Varshney, 2020). Hence, in this study, using the probability technique, an attempt has been made to highlight the effect of "alarm" in overcoming some of the identified obstacles of medication adherence. A probabilistic estimate has been made to see its impact on increased adherence.

BACKGROUND

Non-adherence has been ascribed to a mishmash of factors related to patients' beliefs (Kleppe et al., 2017; Saha et al., 2021b) and practical factors, including resources and capabilities (Basit et al., 2020). Beliefs about medication side effects (Byer & Myers, 2000; Siegel et al., 2000) are positively associated with medication adherence (Perkins et al., 2006). Weight gain is a common side effect of medication that has been reported in many diseases (Blixen et al., 2020; Grandy et al., 2013). Researchers have found a positive correlation between weight gain and medication non-adherence (Khunti et al., 2019; Natashia et al., 2019). Feeling tired or dizzy is a problem that patients and ordinary people face. This may be due to excessive work or medication's side effects (Foster et al., 2014). Generally, people do not follow their medication when they feel tired or dizzy, leading to non-adherence (Valladares-Garrido et al., 2020). An upset stomach is another problem that may happen for several reasons (Behere et al., 2011; Zukiewicz-Sobczak et al., 2013). It has also been associated with side effects due to specific medication (Bartlett et al., 2019). Many researchers think that patients discontinue their medication when they have an upset stomach (Faasse et al., 2015; Yang et al., 2014). In research conducted by Martin et al. (2010), 35% of the respondents reported taking less medication than prescribed due to "running out of medicine". Several researchers reported this as a barrier to medication adherence (Tsega et al., 2015; Varnell et al., 2017). Missing medication dose is again widespread among patients. Studies have reported 69.2% (Venditti et al., 2018), 60% (Habib & Coebergh, 2018), and 53% (Bates et al., 1995) of the patients under study have missed the dose of medication. Many times patients do not complete the course of medicine as prescribed. This could be due to several reasons. In a study of malaria patients, 76% did not meet the course of medication (Khantikul et al., 2009). Several studies have been conducted with alarm as an intervention tool for enhancing medication adherence (Chew et al., 2020; Santo et al., 2019; Varkey et al., 2019). Studies reported an increase in adherence rates using "alarm" as a form of reminder (Brooks et al., 2014; Shen et al., 2019).

In this research, an effort has been made to study the effect of alarm in enhancing medication adherence among patients.

METHODOLOGY

Using the cluster sampling method, a survey was undertaken in Sikkim after taking clearance from the ethical committee of Sikkim Manipal Institute of Medical Sciences (Ref: SMIMS/IEC/2018-064). A questionnaire was designed, and 600 patients were approached between Aug 2019 to April 2020 who received treatment from Central Referral Hospital, Tadong, Gangtok, Sikkim. Out of this, only 525 patients agreed to respond. A sample size above 384 was chosen because, for confidence of 95%, precision of ± 5 and sample proportion of 0.5, for an infinite population, the sample size should be

at least 384. Respondents were asked their agreeableness (yes or no) to the subsequent questions (dependent variable).

1. Would you continue taking your medication even if it leads to weight gain?
2. Would you continue taking your medication even if it causes tiredness or dizziness?
3. Would you continue taking your medication even if it leads to an upset stomach?
4. Do you run out of medicine?
5. Do you miss your medication dose?
6. Do you complete the course of your medication?

They were also asked whether they use alarm (independent variable) for following their medication regime (Yes or No). Responses obtained from the survey were summarized and tabulated in the form of the following table:

In Table 1, a, b, c and d represent the response frequency.

The probability of each question's positive response was calculated for both the cases: "alarm used as a reminder" and "reminder not used", as per the following formula:

$$\hat{p}_{alarm} = \frac{a}{\left(a+b\right)}$$

$$\hat{p}_{no\ reminder} = \frac{c}{\left(c+d\right)}$$

The following formulae were used for finding the risk difference ($\widehat{RD}$), relative risk ($\widehat{RR}$) and odds ratio ($\widehat{OR}$) (Hancock & Kent, 2016)

$$\widehat{RD} = \hat{p}_{alarm} - \hat{p}_{no\ reminder}$$

$$\widehat{RR} = \frac{\hat{p}_{alarm}}{\hat{p}_{no\ reminder}}$$

$$\widehat{OR} = \frac{\frac{\hat{p}_{alarm}}{\left(1-\hat{p}_{alarm}\right)}}{\frac{\hat{p}_{no\ reminder}}{\left(1-\hat{p}_{no\ reminder}\right)}}$$

Table 1. Format for the tabulation of responses

	Alarm used as a reminder	**Reminder not used**	**Total**
Factor's positive response	a	c	a + c
Factor's negative response	b	d	b + d
Total	a + b	c + d	a + b + c + d

For finding a 95% confidence interval (CI), standard error ($\widehat{SE}$) was calculated as per the following formula, and the next subsequent steps were used:

i) For risk difference

$$\widehat{SE}\left(\hat{p}_{alarm}-\hat{p}_{no\ reminder}\right)=\sqrt{\frac{\left(\hat{p}_{alarm}\right)\left(1-\hat{p}_{alarm}\right)}{\left(a+b\right)}+\frac{\left(\hat{p}_{no\ reminder}\right)\left(1-\hat{p}_{no\ reminder}\right)}{\left(c+d\right)}}$$

95% CI is given by:

$$\left(\hat{p}_{alarm}-\hat{p}_{no\ reminder}\right)\pm 2\widehat{SE}\left(\hat{p}_{alarm}-\hat{p}_{no\ reminder}\right)$$

ii) For relative risk

Log of $\widehat{RR}$ is calculated as $\ln(\widehat{RR})$

$$\widehat{SE}\left(\ln(\widehat{RR})\right)=\sqrt{\frac{1}{a}-\frac{1}{\left(a+c\right)}+\frac{1}{b}-\frac{1}{\left(b+d\right)}}$$

95% CI is given by:
$\ln(\widehat{RR})\pm 2\ \widehat{SE}\left(\ln(\widehat{RR})\right)$, anti-log of the values were done to get the values of 95% CI for $\widehat{RR}$

iii) For odds ratio

For this also similar process was used:
Log of $\widehat{OR}$ is calculated as $\ln(\widehat{OR})$

$$\widehat{SE}\left(\ln(\widehat{OR})\right)=\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

95% CI is given by:
$\ln(\widehat{OR})\pm 2\ \widehat{SE}\left(\ln(\widehat{OR})\right)$, anti-log of the values were done to get the values of 95% CI for $\widehat{OR}$

The results obtained were statistically accounted for sampling variability. After determining the standard error, confidence intervals at 95% were estimated, implying that the results are due to the use of alarm and not by chance.

ANALYSIS AND DISCUSSION

The responses obtained for each factor was analyzed as per the above formulae, and after following the steps for calculation of $\widehat{\mathrm{RD}}$ %, $\widehat{\mathrm{RR}}$ %, $\widehat{\mathrm{OR}}$ %, the corresponding standard error was calculated $\widehat{SE}$ %. With the help of $\widehat{SE}$ % values for confidence interval at 95% were calculated. The same results are tabulated below, and their implications are discussed further.

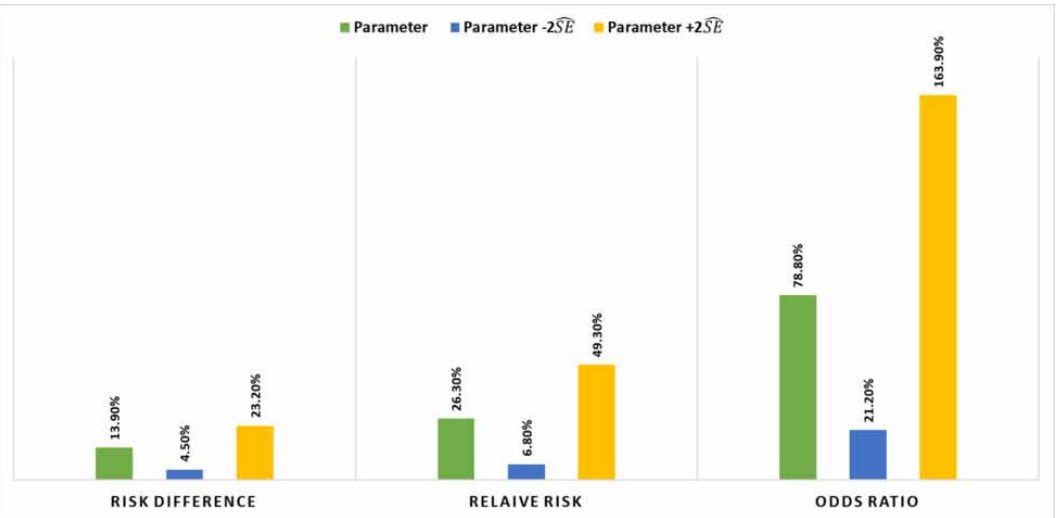
1. Would you continue taking your medication even if it leads to weight gain?

$\widehat{RD}$ = 13.9% signifies that there is a 13.9% absolute likelihood of rise in "continuing medication even if it leads to weight gain" when alarm is used compared to when this form of reminder is not used. CI 95% (4.5%, 23.2%) signifies that when sampling variability is accounted for, the effect of alarm on "continuing medication even if it leads to weight gain" could rise between 4.5% to 23.2%. $\widehat{RR}$ = 26.3% signifies that a person will "continue medication even if it leads to weight gain" is 26.3% higher when an alarm is used compared to when this form of reminder is not used. 95% CI

Table 2. Summary of parameters for weight gain

		CI 95%	
Parameter	Parameter %	Parameter - 2 $\widehat{SE}$	Parameter + 2 $\widehat{SE}$
$\widehat{RD}$	13.9%	4.5%	23.2%
$\widehat{RR}$	26.3%	6.8%	49.3%
$\widehat{OR}$	78.8%	21.2%	163.9%

Figure 1. Graph of parameters for weight gain



(6.8%, 49.3%) signifies that the estimates in probability may rise between 6.8% to 49.3%. $\widehat{OR}$ = 78.8% signifies that patients receiving a reminder in the form of alarm have 78.8% greater odds of "continuing medication even if it leads to weight gain" than when this form of reminder is not used. 95% CI (21.2%, 163.9%) signifies that the estimates in likelihood odds may rise between 21.2% to 163.9%.

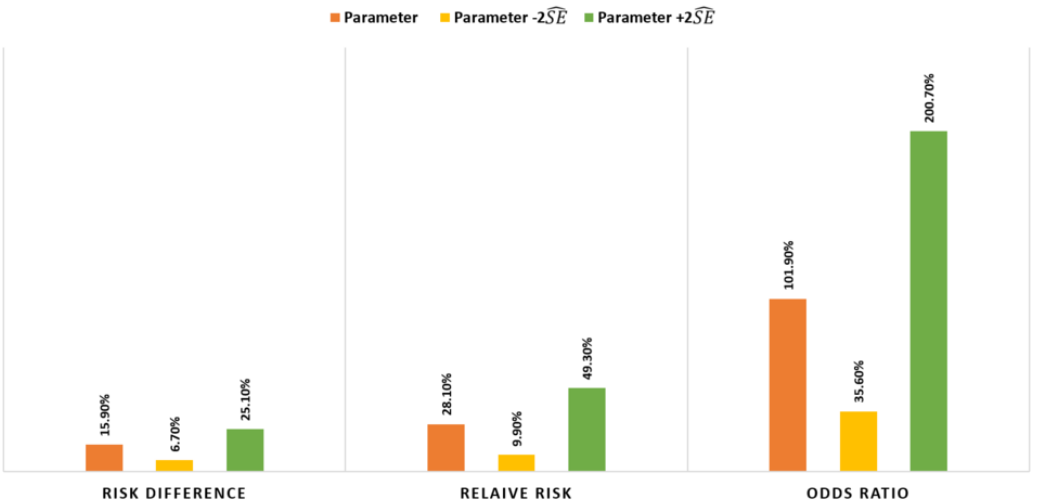
2. Would you continue taking your medication even if it causes tiredness or dizziness?

$\widehat{RD}$ = 15.9% signifies that there is a 15.9% absolute likelihood of rise in "continuing medication even if it causes tiredness or dizziness" when alarm is used compared to when this form of reminder is not used. CI 95% (6.7%, 25.1%) signifies that when sampling variability is accounted for, the alarm effect on "continuing medication even if it causes tiredness or dizzy" could rise between 6.7% to 25.1%. $\widehat{RR}$ = 28.1% signifies that a person will "continue medication even if it causes tiredness or dizzy" is 28.1% higher when an alarm is used compared to when this form of reminder is not used.

Table 3. Summary of parameters for tired or dizzy

		CI 95%	
Parameter	Parameter %	Parameter - 2 $\widehat{SE}$	
Parameter + 2 $\widehat{SE}$	$\widehat{RD}$	15.9%	6.7%
25.1%	$\widehat{RR}$	28.1%	9.9%
49.3%	$\widehat{OR}$	101.9%	35.6%
200.7%			

Figure 2. Graph of parameters for tired or dizzy



95% CI (9.9%, 49.3%) signifies that the estimates in probability may rise between 9.9% to 49.3%. $\widehat{OR}$ = 101.9% signifies that patients receiving a reminder in the form of alarm have 101.9% greater odds of "continuing medication even if it causes tiredness or dizziness" than when this form of reminder is not used. 95% CI (35.6%, 200.7%) signifies that the estimates in likelihood odds may rise between 35.6% to 200.7%.

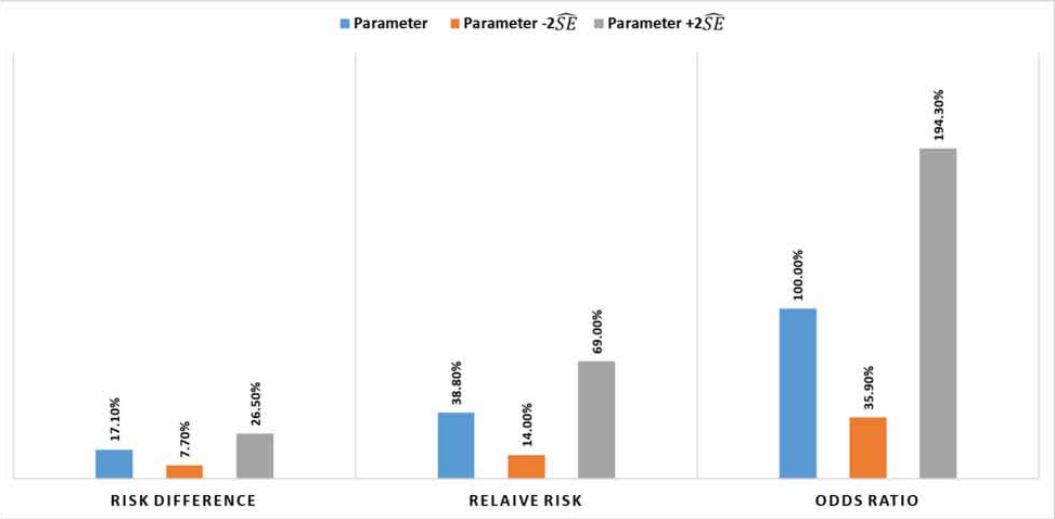
3. Would you continue taking your medication even if it leads to an upset stomach?

$\widehat{RD}$ = 17.1% signifies a 17.1% absolute likelihood of rise in "continuing medication even if it leads to upset stomach" when alarm is used compared to when this form of reminder is not used. CI 95% (7.7%, 26.5%) signifies that when sampling variability is accounted for, the alarm effect on "continuing medication even if it leads to upset stomach" could rise between 7.7% to 26.5%. $\widehat{RR}$ = 38.8% signifies that a patient will "continue medication even if it leads to upset stomach" is 38.8% higher when an alarm is used compared to when this form of reminder is not used. 95% CI (14.0%, 69.0%) signifies that the estimates in probability may rise between 14.0% to 69.0%. $\widehat{OR}$ = 100.0%

Table 4. Summary of parameters for upset stomach

		CI 95%	
Parameter	Parameter %	Parameter - 2 $\widehat{SE}$	Parameter + 2 $\widehat{SE}$
$\widehat{RD}$	17.1%	7.7%	26.5%
$\widehat{RR}$	38.8%	14.0%	69.0%
$\widehat{OR}$	100.0%	35.9%	194.3%

Figure 3. Graph of parameters for upset stomach



signifies that patients who receive a reminder in the form of alarm have 100.0% greater odds of "continuing medication even if it leads to upset stomach" than when this form of reminder is not used. 95% CI (35.9%, 194.3%) signifies that the estimates in likelihood odds may rise between 35.9% to 194.3%.

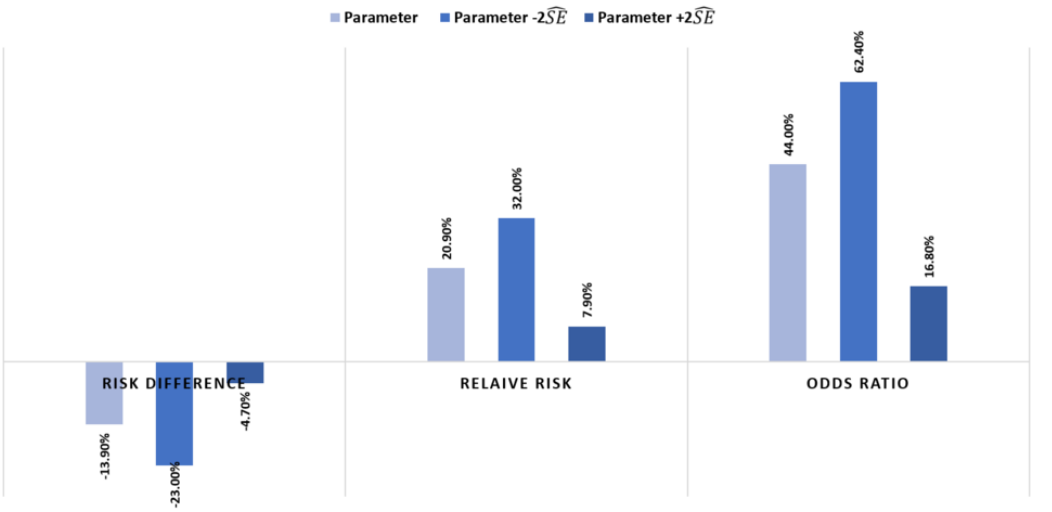
4. Do you run out of medicine?

$\widehat{RD}$ = -13.9% signifies that there is a 13.9% absolute likelihood of falling in "running out of medicine" when alarm is used compared to when this form of reminder is not used. CI 95% (-23.0%, -4.7%) signifies that when sampling variability is accounted for, the alarm effect on "running out of medicine" could decrease between 23.0% to 4.7%. $\widehat{RR}$ = 20.9% signifies that a patient will "run out of medicine" is 20.9% lower when an alarm is used in comparison to when this form of reminder is not used. 95% CI (32.0%, 7.9%) signifies that the estimates in probability may decrease between 7.9% to 32.0%. $\widehat{OR}$ = 44.0% signifies that patients who receive a reminder in the form of alarm have 44.0% lower odds of "running out of medicine" than when this form of reminder is not used. 95%

Table 5. Summary of parameters for running out of medicine

		CI 95%	
Parameter	Parameter %	Parameter - 2 $\widehat{SE}$	Parameter + 2 $\widehat{SE}$
$\widehat{RD}$	-13.9%	-23.0%	-4.7%
$\widehat{RR}$	20.9%	32.0%	7.9%
$\widehat{OR}$	44.0%	62.4%	16.8%

Figure 4. Graph of parameters for running out of medicine



CI (62.4%, 16.8%) signifies that the estimates in likelihood odds may decrease between 16.8% to 62.4%.

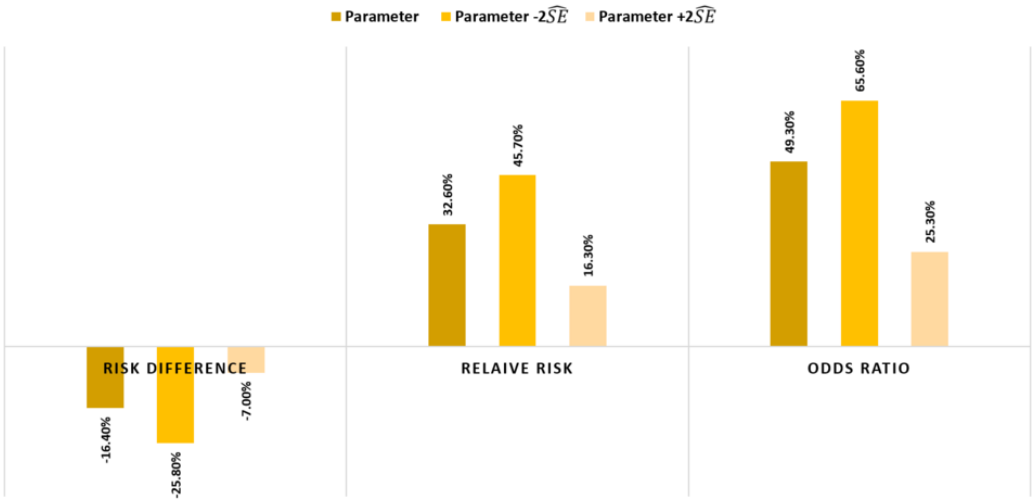
5. Do you miss your medication dose?

$\widehat{RD}$ = -16.4% signifies that there is a 16.4% absolute likelihood of decrease in "missing the medication dose" when alarm is used compared to when this form of reminder is not used. CI 95% (-25.8%, -7.0%) signifies that when sampling variability is accounted for, the alarm effect on "missing the medication dose" could decrease between 25.8% to 7.0%. $\widehat{RR}$ = 32.6% signifies that a patient will "miss the medication dose" is 32.6% lower when an alarm is used in comparison to when this form of reminder is not used. 95% CI (45.7%, 16.3%) signifies that the estimates in likelihood may decrease between 16.3% to 45.7%. $\widehat{OR}$ = 49.3% signifies that patients who receive a reminder in the form of alarm have 49.3% lower odds of "missing the medication dose" than when this form of reminder is not used. 95% CI (65.6%, 25.3%) signifies that the estimates in likelihood odds may decrease between 25.3% to 65.6%.

Table 6. Summary of parameters for missing medication dose

		CI 95%	
Parameter	Parameter %	Parameter - 2 $\widehat{SE}$	Parameter + 2 $\widehat{SE}$
$\widehat{RD}$	-16.4%	-25.8%	-7.0%
$\widehat{RR}$	32.6%	45.7%	16.3%
$\widehat{OR}$	49.3%	65.6%	25.3%

Figure 5. Graph of parameters for missing medication dose



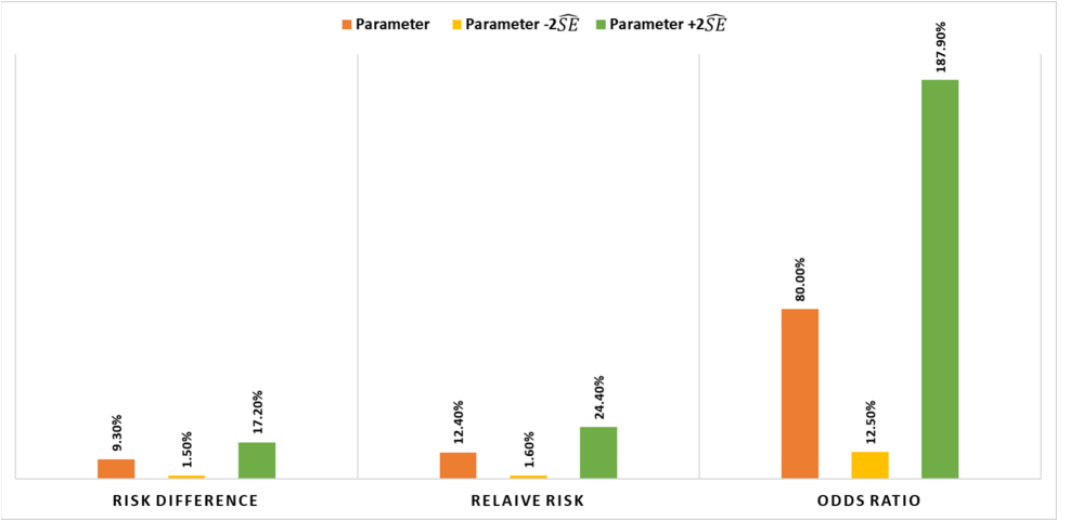
6. Do you complete the course of your medication?

$\widehat{RD}$ = 9.3% signifies that there is a 9.3% absolute likelihood of rise in "completing the course of medication" when alarm is used compared to when this form of reminder is not used. CI 95% (1.5%, 17.2%) signifies that when sampling variability is accounted for, the alarm effect on "completing the course of medication" could rise between 1.5% to 17.2%. $\widehat{RR}$ = 12.4% signifies that a patient will "complete the course of medication" is 12.4% higher when an alarm is used compared to when this form of reminder is not used. 95% CI (1.6%, 24.4%) signifies that the estimates in likelihood may rise between 1.6% to 24.4%. $\widehat{OR}$ = 80.0% signifies that patients who receive a reminder in the form of alarm have 80.0% greater odds of "completing the course of medication" than when this form of reminder is not used. 95% CI (12.5%, 187.9%) signifies that the estimates in likelihood odds may rise between 12.5% to 187.9%.

Table 7. Summary of parameters for completing a course of medicine

		CI 95%	
Parameter	Parameter %	Parameter - 2 $\widehat{SE}$	Parameter + 2 $\widehat{SE}$
$\widehat{RD}$	9.3%	1.5%	17.2%
$\widehat{RR}$	12.4%	1.6%	24.4%
$\widehat{OR}$	80.0%	12.5%	187.9%

Figure 6. Graph of parameters for completing the course of medicine



NOVELTY/SIGNIFICANCE OF THE WORK

- Risk difference, odds ratio and relative risk have been used in the study to check the effectiveness of alarm as an intervention to increase medication adherence.
- Alarm as a form of intervention has been studied on six different factors.
- Probability statistics for groups and individuals have been made in the study.

LIMITATIONS

- Like every research, this study also had certain boundaries. It was limited to a single intervention of alarm.
- The parameters taken for the study was limited to six and was confined to a small geographical area of Sikkim.

FUTURE RESEARCH DIRECTIONS

- More factors can be taken into account to study the effectiveness of interventions.
- Studies with large sample sizes across varied geographical regions can bring more insights into the effectiveness of different intervention techniques across demographic characteristics of patients.
- Future studies can test the effectiveness of multiple interventions like alarms, TV/radio programmes and other electronic gadgets.

RECOMMENDATIONS

- Alarms in family members' mobile devices can also be set who stay with the patients.
- Including reminders with day to day habits of the patients, like taking breakfast, watching a definite television programme or listening to a radio programme, can also prove to be effective.

CONCLUSION

From the results obtained, $\widehat{RD}\,\%$ may not appear to be very high, but upon scaling up for a larger population, a significantly large number of people could be affected by the alarm intervention. For a population of 1000 patients, 139 more patients would be "continuing medication even if it leads to weight gain". The number may vary between 45 to 232. Again for a population of 1000 patients, 159 more patients would be "continuing medication even if it causes tiredness or dizziness", and this number may vary between 67 to 251. One hundred seventy-one more patients are expected to "continue medication even if it leads to upset stomach". This number may vary between 77 to 265. One hundred thirty-nine fewer patients would "run out of medicine" when an alarm is used, and this number may vary between 47 to 230. 164 less number of patients would "miss the medication dose". This number may vary between 70 to 258. Ninety-three more patients would "complete their course of medication", and this number may vary between 15 to 172. All these numbers could be achieved when an alarm is used as a reminder. Other studies conducted using similar methods suggest significant improvement in benefits due to adherence: hospitalization rates decreased by 33% (Kim et al., 2016) and 15%

reduction in the odds (Lage & Hassan, 2009). Increase in odds of adherence with each increase in the year of age by 3% (Ramli et al., 2012).

A randomized controlled clinical trial was conducted in Mombasa, Kenya and women were given multi-vitamins in an electronic medication vial for one month. It was found that compliance was high among the group which received electronic vials (82% vs 36%, $P < 0.001$) (Frick et al., 2001). In another study, statin medication adherence improved significantly when patients were given medication intervention over those who did not receive the intervention (89% vs 67%) (Reddy et al., 2017). Recently, the study conducted by Vieira et al. (2021) also found significant improvement in medication adherence among older adults suffering from hypertension when given alarm intervention through an electronic medication organizer device.

Hence, with the help of a simple intervention like an alarm that is readily available in mobile, wall clock, wrist watch, etc., medication adherence rates can be improved (Bennett et al., 2017; Saha et al., 2022a). Future studies can be directed towards the use of other types of intervention to overcome non-adherence. Also, using an amalgamation of different interventions in improving adherence can be studied. As medication adherence is a complex patient behaviour, several challenges need to be addressed. Patient beliefs, perception towards side effects of medication, etc., remains a challenge to overcome. Judicious use of intervention techniques taking help from electronic gadgets will help increase patients' adherence rate.

FUNDING

This research was funded by the All India Council for Technical Education (AICTE), India, under Research Promotion Scheme for North Eastern Region (RPS-NER) for the grant entitled "Impact of Active Reminders on Medication Adherence" as per letter No 8-104/RIFD/RPS-NER/Policy-1/2019-19 dated 14 March 2019.

The publisher has waived the Open Access Processing fee for this article.

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APPENDIX A - ANNEXURE

Ethical Committee Certificate of Sikkim Manipal Institute of Medical Sciences, Sikkim (Ref: SMIMS/IEC/2018-064)
URL of Ethical Committee Certificate:
https://smu.edu.in/content/dam/manipal/smu/smit/documents/research/ActiveReminders/Ethical%20Committee%20Clearence%20Certificate.jpg
URL of Central Referral Hospital, Tadong, Gangtok, Sikkim approval letter for conducting the survey:
https://smu.edu.in/content/dam/manipal/smu/smit/documents/research/ActiveReminders/CRH%20Approval.jpg
Patient Consent Form:
https://smu.edu.in/content/dam/manipal/smu/smit/documents/research/ActiveReminders/Consent%20form%20for%20patients.pdf

Saibal Kumar Saha (UGC NET Qualified) holds a first class Master's degree in MBA and a first class Bachelor's Degree in Electronics and Communication Engineering. He has 11+ years of experience and has worked in MNCs like Cognizant Technology Solutions and Tata Aig Life. He has served National Institute of Technology - Silchar, Jyotirmoy School of Business – Kolkata, University of Technology and Management - Shillong, Sikkim Manipal Institute of Technology and is presently working as Associate Professor at Christ University, India.

Anindita Adhikary is currently a Professor in Management, Sikkim Manipal University, India. A commerce graduate from Gauhati University, India, she happens to be an MBA from Tezpur Central University, India and was awarded Doctorate by Gauhati University in 2009. Dr. Adhikary has 20 years of professional experience in academics and corporate sector. She has 60+ research publications (select papers in Scopus) to her credit and has been abroad a number of times in order to have an enriched exposure at international level. Dr. Adhikary had participated in 20 professional workshops and delivered talks as Guest Speaker at different Orientation Programmes initiated through National Productivity Council, MSME, Govt. of India and Department of Commerce. Govt. of Sikkim. Her domain of interest includes Finance and International Trade.

Sangita Saha is MBA master from Sikkim Manipal Institute of Technology and BCA graduate from Indira Gandhi National Open University. She has specialized in Human Resource Management and Marketing Management. She has active interest in academic research and her area of interest includes motivation, consumer behavior, tourism and digital technologies. She has worked as Visiting Faculty in the department of Management, MIT University of Meghalaya and is currently pursuing Ph.D from Sikkim Manipal Institute of Technology.

Bedanta Bora is presently engaged as Head-Management Studies at Sikkim Manipal University, India. Graduated in Commerce from Gauhati University, India, he received his MBA degree from Tezpur Central University, India. He was awarded Ph.D by Gauhati University in 2010. Dr. Bora possesses 21 years of professional exposure. He has to his credit around 65+ research papers (select publications in Scopus) with participation in 22 professional workshops and 35 academic conferences held across the world. As far as global exposure is concerned, Dr. Bora has been abroad quite a few times in order to join and host International Conferences as a contributor, committee member, track chair, invited speaker and privileged enough to delivered few key note address as well. He claimed some Best Paper Awards too.