A COSINOR Model Approach to Variation in Seasonality of Number of Patients Enrollment at the Adult ART Clinic

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Abstract: **Objective: This study aims to explore broadly the seasonal variation of the number of patients' enrollment at the adult antiretroviral treatment (ART) clinic, University College Hospital, Ibadan, Nigeria. It also described the variations in seasonality distinctly for the segment 2006-2008, 2009-2011, 2012-2014, 2015-2017 and 2006-2017 in order to ascertain whether there have been changes in time of maxima over the years**

Methods: Analysis of data extracted from electronic records of adult patients enrolled for HIV/AIDS care and treatment at the ART clinic, University College Hospital, Ibadan which covers a period from January 2006 to December 2017 spanning twelve years. Variations on seasonality was investigated using COSINOR model approach.

Results: There was a steady decrease in mean number of patients' enrollment from 212 in 2006-2008 to 63 in 2015-2017 which accounted for about 7% extent of seasonal variation above and below the annual mean with the estimated peak occurring in the month of October. The extent of the seasonal variations above and below the mean level was about 7%, 11%, 16% and 10% in 2006-2008, 2009-2011, 2012-2014 and 2015-2017 respectively.

Conclusion: The entire model fitted for the COSINOR model had a good fit $(p < 0.05)$ except for the year 2006-2008 which is not statistically significant. The seasonal variation in the number of patients enrollment rate showed the peak relatively constant for the last quarter of the first nine years but later shifted to May , that is, the second quarter of the year for the last three years. Changing in seasonal pattern may be as a result of changes in funding cycles in Nigeria by the Federal government because more financial resources are being allocated for the procurement of the medicines.

Keywords**: COSINOR, ART, enrollment, seasonal variation.**

I. INTRODUCTION

The cosinor models introduced by Halberg et al. (1967) and Nelson et. al (1979) and was used to model seasonality. It captures a seasonal pattern using sinusoid and suitable for relatively seasonal patterns that are symmetric and stationary. It is used in diverse applications to fit one or more cosine curves of a given period to rhythmic data [Elkum and Myles (2006); Klisch et al. (2006); Nikhil et al (2007). The percentage of the total variance in the time series data explained by the cosine-curve-model approximation of the given period may be evaluated with R^2as a goodness-of-fit statistic. Cosinor models are characterized by the following parameters: mesor (the rhythm-adjusted mean), amplitude (one half of the peak-to-trough variability of the fitted curve) and acrophase (peak time of the fitted curve relative to midnight).

Among newly enrolled HIV infected persons in almost a decade, more than 1 out of every 10 is an older adult (Chia et al. [1999]).In Sub-Saharan Africa, services for HIV care and treatment have expanded rapidly over the past decade and have provided life-saving ART to cover 2Million infected Adults and Children (WHO, 2008).

In Nigeria only 1 out of 3 people in need of the life-saving ART drugs is accessing treatment compared to South Africa where 2 out of 3 persons in need are accessing treatment (NACA 2017). Several studies have shown that if PLHIV stopped taking ART they will develop AIDS and will die within one year. Others indicate that delay or interruption in the therapy will lead to drug resistance, making the firstline drugs ineffective and the need of secondline medication, which is usually very expensive and unaffordable.

HIV/AIDS remains one of the lethal diseases which cause millions of deaths in a year since the first case report in 1981 (UNAIDS 2013). Much has been done on the HIV/AIDS in different parts of the world but this epidemic infectious disease remains one of the numerous health problems issue in developing countries affecting the working age cohort group of the population. This is due to mainly its intractable mode of transmission and nature of the disease. UNAIDS and WHO (2010) has reported that more than 40million people have been infected with HIV worldwide since the beginning of the epidemic and an estimated 70% of those infected people live in Africa.

Abiola et al (2012) presented a time series analysis of admission in the Accident and Emergency unit of UCH, Ibadan using COSINOR model. The results of the analysis showed that patient's admission peaked in May and minimal in November and the seasonal index showed that the peak of number of patients admitted was observed in the last quarter of the year.

Ezekiel and Leo (2008) used Geographic Information Systems (GIS) to model and forecast HIV/AIDS rate in Africa. Their results indicate that the HIV/AIDS epidemic for many countries in Africa has reached the saturation or maturity level as evidenced by the typical S-Shaped curves in the trends over time. As a matter of fact some countries have begun to experience a sustained decline in the rate, countries like Uganda, Burundi, Rwanda and Zimbabwe.

Curtis and James (2011) reviewed prediction models from nonclinical domains that employ time series data to predict model for cardiac arrest in a pediatric intensive care unit. They proposed a successful prediction model for the phenomenon based on automatic technique that could be used to monitor patients continuously for the risk of cardiac arrest.

II. MATERIAL AND METHOD

2.1 Antiretroviral (ART) clinic, UCH Ibadan

The ART clinic at the UCH Ibadan is one of the first twenty-five ART sites established by the Federal Government of Nigeria in 2002 to provide anti-retroviral drugs to HIV/AIDS patients. Thereafter, treatment at the clinic has been supported by President's Emergency Plan for AIDS Relief (PEPFAR) and AIDS Prevention Initiative in Nigeria (APIN). The data was collected among newly enrolled HIV/AIDS clients at the anti-retroviral clinic (ART) of the University College Hospital (UCH)/College of Medicine, Ibadan, South-West Nigeria.

2.2 Study Design

This study used secondary data of patients enrollment at the adult antiretroviral clinic. The data was extracted from electronic records of patients enrolled for HIV/AIDS care and treatment at the ART clinic, University College Hospital, Ibadan, Nigeria

The data for the patients enrollment at the adult antiretroviral clinic covers a period from January 2006 to December 2017 spanning twelve years. Statistical Package for Social Science (SPSS) version 2018 and Excel 2013.

2.3 COSINOR Model

A cosinor model was proposed by Nelson et al. (1979) to model seasonality. This is an appropriate regression technique to fit a trigonometric curve to the data in order to measure seasonal variation. The cosinor model captures a seasonal pattern using sinusoid. It is relatively patterns that are symmetric and stationary.

Cosinor analysis involved representation of data span by the best-fitting cosine function of the form:

$$Y_t = M + A\cos(\omega_t + \theta)\varepsilon_t$$

Where

M is the mean number of patients enrollment per month between January 2006 to December 2017

Y_t is the number of patients enrollment in the t^{th} ordinal month stating from January 2006

A is the amplitude of the data

ω is the frequency of the periodic variation $= 2\pi f$ (since $f = 1/T$ and $T = 12$ months)

θ is the phase which locate the peak

ε_t is the error term

The equation was fitted to the data by conventional least squares regression analysis. The model is transformed into a linear multiple regression of the form

$$Y_t = M + \beta_1 X_{1t} + \beta_2 X_{2t} + \varepsilon_t$$

Where,

$$X_{1t} = \cos(\omega_t)$$

$$X_{2t} = \sin(\omega_t)$$

$$\beta_1 = A\cos\theta$$

$$\beta_2 = -A\sin\theta$$

$$\omega = \frac{2\pi}{T}$$

$A = \sqrt{\left(\beta_1^2 + \beta_2^2\right)}$. where β_1 and β_2 were obtained from normal equation.

M is estimated by $X_t = \frac{1}{N}\sum_{t=1}^{N} X_t$

$$\beta_1 = \frac{2}{N}\sum_{t=1}^{N} X_t \cos\omega t$$

$$\beta_2 = \frac{2}{N}\sum_{t=1}^{N} X_t \sin\omega t$$

The time of the highest variation is obtained by solving the equation

$$t = \frac{\pi - \theta}{\omega}$$

The estimate of θ is given by

$$\frac{\beta_2}{\beta_1} = -\tan\theta$$

$$\theta = \tan^{-1}\left(-\frac{\beta_2}{\beta_1}\right) \text{ if } \beta_1 > 0$$

But if

$$\beta_1 = 0, \quad \beta_2 > 0 \qquad \theta = -\frac{\pi}{2}$$

$$\beta_1 = 0, \quad \beta_2 < 0 \qquad \theta = -\frac{\pi}{2}$$

$$\beta_1 < 0, \quad \beta_2 < 0 \qquad \theta = \pi + \tan^{-1}\left(-\frac{\beta_2}{\beta_1}\right)$$

$$\beta_1 < 0, \quad \beta_2 > 0 \qquad \theta = \tan^{-1}\left(-\frac{\beta_2}{\beta_1}\right) - \pi$$

(Bloomfield 1976)

The extent of the seasonal variation above the mean level is measured by $\frac{A}{M}$ while the time of the highest variation is obtained by solving the equation $\cos\pi = 0$, where $\pi = \omega t + \theta$. This was converted to months and days.

Hence,

$$t_{\max} = \frac{\pi - \theta}{\omega} = T\left(0.5 - \frac{\theta}{2\pi}\right)$$

The trigonometric techniques used are

$$\sum \cos\omega_p t = \sum \sin\omega_p t = 0$$

$$\sum \cos\omega_p t \cos\omega_p t = \begin{cases} 0 & p \neq q \\ N & p = q = \frac{N}{2} \\ \frac{N}{2} & p = q \neq \frac{N}{2} \end{cases}$$

Taking,

$\sum \cos\omega_p t \sin\omega_p t = 0$ for every p and q

Then,

$$\varepsilon_t^2 = \sum_{i=1}^{N}\left(Y_i - M - \beta_1\cos\omega_t - \beta_2\sin\omega_t\right)^2$$

Where ε_t^2 is an error term square and $p = q \neq \frac{N}{2}$

By Least Squares method,

Differentiate equation 1 with respect to β_1

$$\frac{\partial\varepsilon^2}{\partial\beta_1} = M\sum\cos\omega t - \sum Y_i\cos\omega t + \beta_1\sum\cos\omega t\cos\omega t + \beta_2\sum\sin\omega t\cos\omega t$$

$$0 = \beta_1\left(\frac{N}{2}\right) - \sum Y_i\cos\omega t$$

$$\therefore \beta_1 = \frac{2}{N}\sum Y_i\cos\omega t$$

Differentiate equation 1 with respect to β_2

$$\frac{\partial\varepsilon^2}{\partial\beta_2} = M\sum\sin\omega t - \sum Y_i\sin\omega t + \beta_1\sum\cos\omega t\sin\omega t + \beta_2\sum\sin\omega t\sin\omega t$$

$$0 = \beta_2\left(\frac{N}{2}\right) - \sum Y_i\sin\omega t$$

$$\therefore \beta_2 = \frac{2}{N}\sum Y_i\sin\omega t$$

III. RESULTS AND DISCUSSION

Table 3.1: Distribution of number of patients enrolled per month, 2006-2007

Year	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	TOTAL
2006	138	159	200	153	237	214	216	239	192	200	247	160	2355
2007	183	285	196	202	275	240	209	325	219	247	258	159	2798
2008	273	266	231	279	251	117	211	195	166	179	194	124	2486
2009	199	143	192	198	179	219	170	157	148	144	134	169	2052
2010	149	166	199	156	142	138	172	207	113	151	152	159	1904
2011	137	105	185	144	194	176	146	139	162	133	134	127	1782
2012	95	157	165	158	141	138	142	130	129	94	138	137	1624
2013	156	124	94	116	97	85	109	116	105	83	78	91	1254
2014	97	103	133	91	109	131	61	52	88	72	76	60	1073
2015	68	65	86	73	41	59	52	61	83	59	88	69	804
2016	95	67	58	51	60	53	58	78	64	73	75	63	795

2017	70	63	53	50	61	55	62	63	51	59	58	34	679
TOTAL	1660	1703	1792	1671	1787	1625	1608	1762	1520	1494	1632	1352	19606

Table 3.2: Corrected monthly patients' enrolments for all series

Year	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	TOTAL
2006-2008	594	710	627	634	763	571	636	759	577	626	699	443	7639
2009-2011	485	414	576	498	515	533	488	503	423	428	420	455	5738
2012-2014	348	384	392	365	347	354	312	298	322	249	292	288	3951
2015-2017	233	195	197	174	162	167	172	202	198	191	221	166	2278
2006-2017	1660	1703	1792	1671	1787	1625	1608	1762	1520	1494	1632	1352	19606

Table 3.2 above shows the data presented in a 3 – years series.

3.3 Trigonometric Regression (COSINOR) Analysis of Patients' Enrollment

3.3.1 Analysis for the first time segment (2006-2008)

$$\omega = \frac{2\pi}{T}$$
$$= \frac{(2 * 3.142)}{12}$$
$$= 0.5237$$

$$\beta_1 = \frac{2}{36}\sum_{i=1}^{36} X_t \cos\omega t$$
$$= 0.0556 * (-247.3777)$$
$$= -13.7542$$

$$\beta_2 = \frac{2}{36}\sum_{i=1}^{36} X_t \sin\omega t$$
$$= 0.0556 * 25.4921$$
$$= 1.4162$$

$$A = \sqrt{\beta_1^2 + \beta_2^2}$$
$$= \sqrt{(-13.7542)^2 + (1.4162)^2}$$
$$= \sqrt{189.1780 + 2.0056}$$
$$= \sqrt{191.1836}$$
$$= 13.8269$$

Since $\beta_1 < 0$, $\beta_2 > 0$

$$\theta = \tan^{-1}\left(-\frac{\beta_2}{\beta_1}\right) - \pi$$
$$= \tan^{-1}\left(-\frac{1.4162}{-13.7542}\right) - 3.143$$
$$= \tan^{-1}(0.1030) - 3.143$$
$$= -3.0404$$

$$M = \frac{1}{36}\sum_{t=1}^{36} X_t$$
$$= \frac{769}{36}$$
$$= 212.19$$

The extent of the seasonal variation above and below the annual mean level was measured by

$$\frac{A}{M} = \frac{13.8269}{212.19}$$
$$= 0.0652$$

$$t = \frac{\pi - \theta}{\omega}$$
$$= \frac{3.1429 + 3.0404}{0.5237}$$
$$= 11.8070$$

3.3.2 Analysis for the second time segment (2009-2011)

$$\omega = \frac{2\pi}{T}$$
$$= \frac{(2 * 3.142)}{12}$$
$$= 0.5237$$

$$\beta_1 = \frac{2}{36}\sum_{t=1}^{36} X_t \cos\omega t$$
$$= 0.0556 * (-241.5435)$$
$$= -13.4298$$

$$\beta_2 = \frac{2}{36}\sum_{t=1}^{36} X_t \sin\omega t$$
$$= 0.0556 * 182.3175$$
$$= 10.1369$$

$$A = \sqrt{\beta_1^2 + \beta_2^2}$$

$$= \sqrt{(-13.4298)^2 + (10.1369)^2}$$
$$= \sqrt{173.6597 + 102.7567}$$
$$= \sqrt{276.4164}$$
$$= 16.8281$$

Since $\beta_1 < 0$, $\beta_2 > 0$

$$\theta = \tan^{-1}\left(-\frac{\beta_2}{\beta_1}\right) - \pi$$
$$= \tan^{-1}\left(-\frac{10.1369}{-13.4298}\right) - 3.14289$$
$$= \tan^{-1}(0.7548) - 3.1429$$
$$= -2.4963$$
$$M = \frac{1}{36}\sum_{t=1}^{36} X_t$$
$$= \frac{578}{36}$$
$$= 159.39$$
$$\frac{A}{M} = \frac{16.8281}{159.39}$$
$$= 0.1056$$
$$t = \frac{\pi - \theta}{\omega}$$
$$= \frac{3.1429 + 2.4964}{0.5237}$$
$$= 10.7681$$

3.3.3 Analysis for the third time segment (2012-2014)

$$\omega = \frac{2\pi}{T}$$
$$= \frac{(2 * 3.142)}{12}$$
$$= 0.5237$$
$$\beta_1 = \frac{2}{36}\sum_{i=1}^{36} X_t \cos\omega t$$
$$= 0.0556 * (-97.2909)$$
$$= -5.4094$$
$$\beta_2 = \frac{2}{36}\sum_{i=1}^{36} X_t \sin\omega t$$
$$= 0.0556 * 290.4056$$
$$= 16.1466$$
$$A = \sqrt{\beta_1^2 + \beta_2^2}$$
$$= \sqrt{(-5.4094)^2 + (16.1466)^2}$$
$$= \sqrt{29.2616 + 260.7127}$$
$$= \sqrt{289.9743}$$
$$= 17.0286$$

Since $\beta_1 < 0$, $\beta_2 > 0$

$$\theta = \tan^{-1}\left(-\frac{\beta_2}{\beta_1}\right) - \pi$$
$$= \tan^{-1}\left(-\frac{16.1466}{-5.4094}\right) - 3.1429$$
$$= \tan^{-1}(2.9849) - 3.1429$$
$$= -1.8954$$
$$M = \frac{1}{36}\sum_{t=1}^{36} X_t$$
$$= \frac{3951}{36}$$
$$= 109.75$$
$$\frac{A}{M} = \frac{17.0286}{109.75}$$
$$= 0.1552$$
$$t = \frac{\pi - \theta}{\omega}$$
$$= \frac{3.1429 + 1.8954}{0.5237}$$
$$= 9.6208$$

3.3.4 Analysis for the fourth time segment (2015-2017)

$$\omega = \frac{2\pi}{T}$$
$$= \frac{(2 * 3.142)}{12}$$
$$= 0.5237$$
$$\beta_1 = \frac{2}{36}\sum_{i=1}^{36} X_t \cos\omega t$$
$$= 0.0556 * (108.4178)$$
$$= 6.02804$$
$$\beta_2 = \frac{2}{36}\sum_{i=1}^{36} X_t \sin\omega t$$
$$= 0.0556 * (-20.5832)$$
$$= -1.1444$$
$$A = \sqrt{\beta_1^2 + \beta_2^2}$$

$$= \sqrt{6.0280^2 + (-1.1444)^2}$$
$$= \sqrt{36.3368 + 1.3097}$$
$$= \sqrt{37.6465}$$
$$= 6.1358$$

Since $\beta_1 > 0$,

$$\theta = \tan^{-1}\left(-\frac{\beta_2}{\beta_1}\right)$$
$$= \tan^{-1}\left(-\frac{-1.1444}{6.0280}\right)$$
$$= \tan^{-1}(0.1898)$$
$$= 0.1876$$
$$M = \frac{1}{36}\sum_{t=1}^{36} X_t$$
$$= \frac{2278}{36}$$
$$= 63.28$$
$$\frac{A}{M} = \frac{6.1358}{63.28}$$
$$= 0.0970$$
$$t = \frac{\pi - \theta}{\omega}$$
$$= \frac{3.1429 - 0.1876}{0.5237}$$
$$= 5.6431$$

3.3.5 Analysis for the whole time segment (2006-2017)

$$\omega = \frac{2\pi}{T}$$
$$= \frac{(2 * 3.142)}{12}$$
$$= 0.5237$$
$$\beta_1 = \frac{2}{144}\sum_{t=1}^{144} X_t \cos\omega t$$
$$= 0.0139 * (-480.3524)$$
$$= -6.6769$$
$$\beta_2 = \frac{2}{144}\sum_{t=1}^{144} X_t \sin\omega t$$
$$= 0.0139 * 477.2203$$
$$= 6.6334$$
$$A = \sqrt{\beta_1^2 + \beta_2^2}$$
$$= \sqrt{(-6.6769)^2 + (6.6334)^2}$$
$$= \sqrt{44.5810 + 44.0020}$$
$$= \sqrt{88.583}$$
$$= 9.4119$$

Since $\beta_1 < 0$, $\beta_2 > 0$

$$\theta = \tan^{-1}\left(-\frac{\beta_2}{\beta_1}\right) - \pi$$
$$= \tan^{-1}\left(-\frac{6.6334}{-6.6769}\right) - 3.1429$$
$$= \tan^{-1}(0.9935) - 3.1429$$
$$= -2.3608$$
$$M = \frac{1}{144}\sum_{t=1}^{144} X_t$$
$$= \frac{19606}{144}$$
$$= 136.15$$
$$\frac{A}{M} = \frac{9.4119}{136.15}$$
$$= 0.0691$$
$$t = \frac{\pi - \theta}{\omega}$$
$$= \frac{3.1429 + 2.3609}{0.5237}$$
$$= 10.5096$$

Table 3.3 below shows the results of Trigonometric Regression for each 3-year period of the four time segments and the entire period as a whole after adjusting the trend. The entire model fitted for the trigonometric regression had a good fit $(p < 0.05)$ except for the year 2006-2008 which is not statistically significant.

There was a steady decrease in mean number of patients' enrollment from 212 in 2006-2008 to 63 in 2015-2017 which accounted for about 7% extent of seasonal variation above and below the annual mean with the estimated peak occurring in the month of October. The extent of the seasonal variations above and below the mean level was about 7%, 11%, 16% and 10% in 2006-2008, 2009-2011, 2012-2014 and 2015-2017 respectively. The estimated month of the peak was in November for the first time segment (2006-2008), October for the second time segment (2009-2011), September for the third time segment (2012-2014) and May for the fourth time segment (2015-2017). The magnitude of the variation was 16% high and 7% low above and below the annual mean.

Table 3.3: Results of Trigonometric Regression Analysis on Patients' Enrollment, 2006-2017

Period	F	P	M	A	$\frac{A}{M}$	θ	t	Month of Peak
2006-2008	0.0350	0.852	212.19	13.8269	0.0652	-3.1430	11.8070	November
2009-2011	7.0250	0.012	159.39	16.8281	0.1056	-2.4963	10.7684	October
2012-2014	38.355	0.000	109.75	17.0286	0.1552	-1.8954	9.6208	September
2015-2017	4.8800	0.034	63.28	6.1358	0.0969	0.1876	5.6387	May
2006-2017	466.045	0.000	136.15	9.4119	0.0691	-2.3608	10.5096	October

IV. CONCLUSION

It was revealed that the peak of number of adult patients enrolled at the ART clinic was observed majorly toward the last quarter of the every year, that is, September, October and November. Intensify efforts for urgent scaling up of core HIV prevention measures which include use of condoms, harm reduction, pre expose prophylaxis, voluntary medical male circumcision and behavior change along with global efforts to provide HIV treatments for all people living with it. The opportunity to end the AIDS epidemic hinges on the combined force of all prevention tools and approaches while also giving people the opportunity to use the method (or methods) of their choice. The yearly targets should be based on the sort of evidence provided in this study. The clinic managers can be alerted to plan adequately for the upsurge in patients enrollment in the last quarter of the year.

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Appendix

Table 1: Components of the Trigonometric Regression of the patients' enrollment for 2006-2008

t	X_t	$X_t \sin \omega t$	$X_t \cos \omega t$
1	138	69.0121	119.5045
2	159	137.7141	79.4721
3	200	200.0000	-0.0607
4	153	132.4709	-76.5536
5	237	118.3961	-205.3080
6	214	-0.1300	-214.0000
7	216	-108.1325	-186.9849
8	239	-207.0768	-119.3323
9	192	-191.9999	0.1749
10	200	-173.1038	100.1753
11	247	-123.2617	214.0457
12	160	0.1944	159.9999
13	183	91.7085	158.3621
14	285	247.0189	142.1501
15	196	195.9998	-0.2976
16	202	174.7733	-101.2832
17	275	137.0900	-238.3932
18	240	-0.4373	-239.9996
19	209	-104.8479	-180.7980
20	325	-281.7867	-161.9299
21	219	-218.9995	0.4655
22	247	-213.6327	123.9761
23	258	-128.4795	223.7343
24	159	0.3863	158.9995
25	273	137.0979	236.0788
26	266	230.7120	132.3933
27	231	230.9991	-0.6313
28	279	241.2247	-140.1843
29	251	124.8614	-217.7398
30	117	-0.3553	-116.9995
31	211	-106.0729	-182.3994
32	195	-169.1899	-96.9525

33	166	-165.9991	0.5545
34	179	-154.7096	90.0330
35	194	-96.4042	168.3515
36	124	0.4519	123.9992
∑	**7639**	**25.4921**	**-247.3777**

Table 2: Components of the Trigonometric Regression of the patients' enrollment for 2009-2011

t	X_t	$X_t \sin\omega t$	$X_t \cos\omega t$
37	199	99.5174	172.3290
38	143	123.8561	71.4749
39	192	192.0000	-0.0583
40	198	171.4329	-99.0694
41	179	89.4215	-155.0638
42	219	-0.1330	-219.0000
43	170	-85.1043	-147.1641
44	157	-136.0295	-78.3899
45	148	-147.9999	0.1348
46	144	-124.6347	72.1262
47	134	-66.8707	116.1219
48	169	0.2053	168.9999
49	149	74.6697	128.9396
50	166	143.8777	82.7962
51	199	198.9998	-0.3022
52	156	134.9735	-78.2187
53	142	70.7883	-123.0976
54	138	-0.2514	-137.9998
55	172	-86.2863	-148.7907
56	207	-179.4764	-103.1369
57	113	-112.9997	0.2402
58	151	-130.6014	75.7910
59	152	-75.6933	131.8124
60	159	0.3863	158.9995
61	137	68.8000	118.4718
62	105	91.0705	52.2605
63	185	184.9993	-0.5056

64	144	124.5031	-72.3532
65	194	96.5064	-168.2929
66	176	-0.5345	-175.9992
67	146	-73.3964	-126.2100
68	139	-120.6020	-69.1097
69	162	-161.9991	0.5411
70	133	-114.9518	66.8960
71	134	-66.5884	116.2840
72	127	0.4628	126.9992
$\sum$	**5738**	**182.3175**	**-241.5435**

Table 3: Components of the Trigonometric Regression of the patients ‘enrollment for 2012-2014

t	X_t	$X_t \sin \omega t$	$X_t \cos \omega t$
73	95	47.5083	82.2676
74	157	135.9819	78.4725
75	165	165.0000	-0.0501
76	158	136.8000	-79.0554
77	141	70.4382	-122.1452
78	138	-0.0838	-138.0000
79	142	-71.0871	-122.9253
80	130	-112.6359	-64.9088
81	129	-128.9999	0.1175
82	94	-81.3588	47.0824
83	138	-68.8669	119.5883
84	137	0.1664	136.9999
85	156	78.1777	134.9972
86	124	107.4749	61.8478
87	94	93.9999	-0.1427
88	116	100.3649	-58.1626
89	97	48.3554	-84.0878
90	85	-0.1549	-84.9999
91	109	-54.6814	-94.2918
92	116	-100.5762	-57.7965
93	105	-104.9998	0.2232
94	83	-71.7875	41.6600

95	78	-38.8426	67.6406
96	91	0.2211	90.9997
97	97	48.7124	83.8815
98	103	89.3358	51.2651
99	133	132.9995	-0.3635
100	91	78.6790	-45.7232
101	109	54.2227	-94.5563
102	131	-0.3978	-130.9994
103	61	-30.6656	-52.7316
104	52	-45.1173	-25.8540
105	88	-87.9995	0.2940
106	72	-62.2296	36.2144
107	76	-37.7666	65.9521
108	60	0.2186	59.9996
$\sum$	**3951**	**290.4056**	**-97.2909**

Table 4: Components of the Trigonometric Regression of the patients' enrollment for 2015

t	X_t	$X_t \sin \omega t$	$X_t \cos \omega t$
109	68	34.0060	58.8863
110	65	56.2982	32.4886
111	86	86.0000	-0.0261
112	73	63.2051	-36.5256
113	41	20.4820	-35.5174
114	59	-0.0358	-59.0000
115	52	-26.0319	-45.0149
116	61	-52.8522	-30.4572
117	83	-83.0000	0.0756
118	59	-51.0656	29.5517
119	88	-43.9151	76.2592
120	69	0.0838	68.9999
121	95	47.6082	82.2098
122	67	58.0711	33.4177
123	58	57.9999	-0.0881
124	51	44.1259	-25.5715
125	60	29.9105	-52.0131

126	53	-0.0966	-52.9999
127	58	-29.0966	-50.1736
128	78	-67.6288	-38.8632
129	64	-63.9999	0.1360
130	73	-63.1384	36.6407
131	75	-37.3487	65.0390
132	63	0.1531	62.9998
133	70	35.1533	60.5330
134	63	54.6423	31.3563
135	53	52.9998	-0.1449
136	50	43.2302	-25.1226
137	61	30.3448	-52.9169
138	55	-0.1670	-54.9997
139	62	-31.1683	-53.5960
140	63	-54.6613	-31.3231
141	51	-50.9997	0.1704
142	59	-50.9937	29.6757
143	58	-28.8219	50.3319
144	34	0.1239	33.9998
$\sum$	**2278**	**-20.5832**	**108.4178**

Table 5: Components of the Trigonometric Regression of the patients' enrollment for 2006-2017

t	X_t	$X_t \sin\omega t$	$X_t \cos\omega t$
1	138	69.0121	119.5045
2	159	137.7141	79.4721
3	200	200.0000	-0.0607
4	153	132.4709	-76.5536
5	237	118.3961	-205.3080
6	214	-0.1300	-214.0000
7	216	-108.1325	-186.9849
8	239	-207.0768	-119.3323
9	192	-191.9999	0.1749
10	200	-173.1038	100.1753
11	247	-123.2617	214.0457
12	160	0.1944	159.9999

13	183	91.7085	158.3621
14	285	247.0189	142.1501
15	196	195.9998	-0.2976
16	202	174.7733	-101.2832
17	275	137.0900	-238.3932
18	240	-0.4373	-239.9996
19	209	-104.8479	-180.7980
20	325	-281.7867	-161.9299
21	219	-218.9995	0.4655
22	247	-213.6327	123.9761
23	258	-128.4795	223.7343
24	159	0.3863	158.9995
25	273	137.0979	236.0788
26	266	230.7120	132.3933
27	231	230.9991	-0.6313
28	279	241.2247	-140.1843
29	251	124.8614	-217.7398
30	117	-0.3553	-116.9995
31	211	-106.0729	-182.3994
32	195	-169.1899	-96.9525
33	166	-165.9991	0.5545
34	179	-154.7096	90.0330
35	194	-96.4042	168.3515
36	124	0.4519	123.9992
37	199	100.1448	171.9652
38	143	124.1157	71.0231
39	192	191.9985	-0.7580
40	198	171.0708	-99.6935
41	179	88.8559	-155.3887
42	219	-0.9311	-218.9980
43	170	-85.6400	-146.8530
44	157	-136.3143	-77.8936
45	148	-147.9985	0.6742
46	144	-124.3711	72.5799
47	134	-66.4471	116.3648
48	169	0.8211	168.9980

49	149	75.1391	128.6667
50	166	144.1785	82.2713
51	199	198.9973	-1.0273
52	156	134.6875	-78.7100
53	142	70.3392	-123.3547
54	138	-0.7543	-137.9979
55	172	-86.8280	-148.4753
56	207	-179.8511	-102.4822
57	113	-112.9981	0.6520
58	151	-130.3243	76.2664
59	152	-75.2125	132.0874
60	159	0.9657	158.9971
61	137	69.2313	118.2203
62	105	91.2604	51.9283
63	185	184.9962	-1.1798
64	144	124.2386	-72.8064
65	194	95.8925	-168.6435
66	176	-1.1758	-175.9961
67	146	-73.8558	-125.9417
68	139	-120.8531	-68.6698
69	162	-161.9960	1.1315
70	133	-114.7073	67.3145
71	134	-66.1643	116.5259
72	127	0.9256	126.9966
73	95	48.1066	81.9192
74	157	136.5502	77.4793
75	165	164.9952	-1.2526
76	158	136.2202	-80.0503
77	141	69.5461	-122.6554
78	138	-1.0896	-137.9957
79	142	-71.9811	-122.4039
80	130	-113.1060	-64.0862
81	129	-128.9957	1.0577
82	94	-81.0135	47.6741
83	138	-67.9935	120.0870
84	137	1.1649	136.9950

85	156	79.1595	134.4239
86	124	107.9228	61.0628
87	94	93.9964	-0.8278
88	116	99.9383	-58.8926
89	97	47.7412	-84.4380
90	85	-0.7744	-84.9965
91	109	-55.3672	-93.8907
92	116	-100.9947	-57.0620
93	105	-104.9953	0.9884
94	83	-71.4820	42.1821
95	78	-38.3486	67.9219
96	91	0.8843	90.9957
97	97	49.3225	83.5242
98	103	89.7071	50.6126
99	133	132.9933	-1.3328
100	91	78.3437	-46.2954
101	109	53.5321	-94.9490
102	131	-1.3525	-130.9930
103	61	-31.0491	-52.5067
104	52	-45.3045	-25.5245
105	88	-87.9950	0.9353
106	72	-61.9640	36.6670
107	76	-37.2849	66.2256
108	60	0.6559	59.9964
109	68	34.6477	58.5110
110	65	56.6500	31.8712
111	86	85.9946	-0.9663
112	73	62.8020	-37.2144
113	41	20.0925	-35.7392
114	59	-0.6808	-58.9961
115	52	-26.5225	-44.7276
116	61	-53.1820	-29.8776
117	83	-82.9942	0.9830
118	59	-50.7395	30.1082
119	88	-43.0788	76.7347
120	69	0.8381	68.9949

121	95	48.5041	81.6845
122	67	58.4330	32.7809
123	58	57.9955	-0.7221
124	51	43.8438	-26.0524
125	60	29.3401	-52.3369
126	53	-0.6760	-52.9957
127	58	-29.6433	-49.8525
128	78	-68.0496	-38.1215
129	64	-63.9945	0.8357
130	73	-62.7341	37.3287
131	75	-36.6354	65.4434
132	63	0.8418	62.9944
133	70	35.8129	60.1451
134	63	54.9818	30.7571
135	53	52.9951	-0.7242
136	50	42.9530	-25.5937
137	61	29.7645	-53.2454
138	55	-0.7683	-54.9946
139	62	-31.7524	-53.2521
140	63	-55.0005	-30.7237
141	51	-50.9948	0.7279
142	59	-50.6662	30.2314
143	58	-28.2699	50.6440
144	34	0.4956	33.9964
$\sum$	**19606**	**477.2203**	**-480.3524**