A study on cost-effectiveness of prophylactic and on-demand treatment for Hemophilia A

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By

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List of Acronyms

ABR: Annualized Bleeding Rate

AHF: Antihemophilic Factor (Factor VIII)

BPA: Bypassing Agents

CUA: Cost Utility Analysis

ESIC: Employees' State Insurance Corporation

FRT: Factor Replacement Therapy

GoI: Government of India

HDCC: Hemophilia Day Care Centers

HFI: Hemophilia Federation of India

HR-QoL: Health Related Quality of Life

ICER: Incremental Cost Effectiveness Ratio

INR: Indian National Rupee

IRB: Institutional Review Board

OD: On-Demand

PRO: Prophylaxis

PWH: Persons with Hemophilia

QALY: Quality Adjusted Life Years

QoL: Quality of Life

RCT: Randomized Controlled Trial

WFH: World Federation of Hemophilia

WHO: World Health Organization

Abstract

Introduction: India consists of the maximum number of reported cases of Hemophilia A all over the world. Factor replacement therapy (FRT) is considered as the standard treatment of Hemophilia A, which can be provided as on-demand treatment or as prophylaxis treatment. In India, the government provides on-demand treatment in the public hospitals at present.

Aim: To understand the cost-effectiveness of prophylactic (PRO) treatment option vs on-demand (OD) options of FRT for Hemophilia A among Indian adults. The study intends to present the healthcare payer's perspective about the costs and benefits of both PRO and OD treatment options from India, a resource limited country.

Methods: A Markov Model assesses the lifetime cost-effectiveness of prophylaxis (PRO) vs on-demand (OD) treatment for patient of Hemophilia A, ≥18 years of age, in India for healthcare payer perspective. Input variables were taken from various data sources and published literature. An observational study was done to collect the required patient information on the input variables which were not reported in the literature. Costs of both the treatment were evaluated against QALYs (Quality Adjusted Life Years) as the outcome measure. Costs and QALYs were also calculated for low-dose prophylactic treatment. The analysis was done with discount rates of 5.98% according to the inflation rates of India.

Results: For base case, Incremental Cost Effectiveness Ratio (ICER) was calculated as INR 90,84,164 per QALY and for low-dose prophylaxis case, it was calculated as INR 68,24,294 per QALY.

1. Introduction:

Majority of the genetic conditions are orphan disorders which create substantial distress to the patients and their family members but are rendered less important public health priority in India.[12] These disorders account for recurring hospitalizations and affect the health service delivery.[32] While preventive services are not provided for such disorders due to the opinion that these conditions are rare and self-limiting.[452]These orphan disorders concern a substantial population in India because of the demographic features of the country.[2]The number of people suffering from such diseases is expected to be elevated in India since these diseases occur due to mutations and genetic inheritance.[2]

Hemophilia A, a single gene disorder, manifests as a higher bleeding tendency in the person with Hemophilia (PWH) due to the deficiency in synthesis of clotting factor VIII happening because of mutation in the related gene. PWH experiences recurrent internal bleeding episodes mostly occurring in the joints and soft tissues due to the deficiency of clotting factor. The frequency of occurrence of such bleeding episodes is dependent in the clotting factor levels and the genotype of the PWH. PWH are categorized as having mild hemophilia (5%-40% of factor VIII levels), moderate hemophilia (1%-5% of the factor VIII levels), and severe hemophilia (less than 1% of the factor VIII levels).

India consists of the maximum number of reported cases of Hemophilia A all over the world with an absolute number of 15,920 PWH as reported in Annual Global Survey 2017.[6]It is believed that the actual numbers of PWH in India could go up to 50,000 which go undiagnosed

or non-reported.[2] The standardized treatment of Hemophilia across the world has been Factor Replacement Therapy which involves providing manufactured Factor VIII to the patients to improve the factor VIII deficiency levels in body.[7] FRT can be provided as two treatment options, namely, On-demand treatment option and Prophylactic treatment option.[7] While on-demand treatment option implies to providing factor VIII following a bleeding episode, the other option, prophylactic treatment concerns with providing factor VIII regularly to avoid the occurrence of a bleed.[7] The prophylactic treatment is further categorized into primary, secondary and tertiary prophylaxis.[7] Initiating the prophylactic treatment prior to occurrence of two joint bleeds is known as primary prophylaxis; while starting it after the onset of serial bleeding is known as secondary bleeding; and providing prophylaxis after the development of an established joint damage is termed as tertiary prophylaxis.[7] A major complication of FRT has been identified as the occurrence of inhibitors to the Factor VIII being provided. The occurrence of inhibitors does not differentiate between the type of FRT and has no significant association with either type of treatment option, on demand or prophylaxis.[8]A higher intensity of treatment which involves prolonged exposure to factor VIII, usually happens during trauma or surgery, has been found to increase the risk of development of inhibitors.[8]For the treatment of such cases, bypassing agents (BPA) are provided as the treatment product in place of factor VIII.[8] A common example of BPA is Factor VIIa.[8] The incidence of cases of inhibitor development has been estimated as 33% in patients of Hemophilia A.[8] As per the Global Survey Report 2017, 776 inhibitor cases have been identified in India which is 4.87% of PWH.[6]

In India, on-demand treatment option is being provided, free of cost, in public hospitals at district levels and above. Prophylaxis treatment has shown to decrease the bleeding episodes substantially in prior trials increasing the quality of life of PWH when compared OD treatment.[9] Although the treatment drug, Factor VIII, is included in the essential drug list of public health system delivery in India, shortage of the drug is commonly experienced in the system.[10] As the patients receiving on-demand treatment experience recurrent bleeding episodes, the shortage of drug during extensive and recurring bleedings causes orthopedic morbidity and premature mortality.[10] Higher costs of Factor VIII results in low affordability of the drug and hence PWH are dependent on the public health system for the management of their health conditions. The higher costs of the treatment drug along-with the shortage of drug at public hospitals further worsens the quality of life of PWH and their family members.[11]

2. Rationale:

India has highest number of Hemophilia A patients all over the world with an calculated prevalence of 0.9 per 1,00,000 people (while estimated prevalence could go up-to 4 per 1.00,000).[2]Currently its treatment is provided by the Government of India (GoI) free of cost to the patients. The On-demand therapy is being provided by GoI through Hemophilia Day Care centers and through public hospitals in India. Previous research done using randomized controlled trials has shown Prophylaxis treatment of Hemophilia as more effective than the On-demand option.[912] A significant difference has been observed in various clinical outcomes of patients on prophylaxis vs on-demand treatment. The POTTER study, a randomized controlled trial, by Tagliaferri et al. reports the annualized bleeding rate (ABR) in patients on OD treatment

vs Prophylactic treatment. For younger patients, the ABR was reported as 1.97 in patients on prophylaxis vs 16.80 in patient on OD treatment. For older patients, the ABR was 2.46 in patients on prophylaxis vs 16.71 in patients on OD treatment.[9] A significant difference was also observed in the mean number of days of everyday activities lost per patient/care-giver which was 10.6 for patients on prophylaxis vs 43 for patients receiving OD treatment in the younger age group patients.[9] For older patients, it was observed as 13.8 for patients on prophylaxis vs 35.6 for patients on OD treatment,[9]For countries with resource constraints, prophylaxis treatment can be provided as lower but frequent doses (low dose), as guided by World Federation of Hemophilia (WFH).[13] Guidelines for the management of Hemophilia, 2nd edition, by WFH explains the commonly-used prophylactic dosage for less resource constrained countries as 25-40 IU/kg 2-3 times weekly; and 10-20 IU/kg 2-3 times per week for greater resource constrained countries.[13]Low dose prophylactic treatment has shown outcomes such as highly reduced hospital visits or hospital stay and highly reduced school absenteeism or work absenteeism when compared with on-demand treatment.[14]In Indian context, a very low dose prophylactic therapy has also been found as more effective when compared to the On-demand treatment.[15]The randomized study by Verma et al. comparing very low dose prophylaxis of dosage 10 IU/kg 2 times per week, vs on demand treatment, done in India on children of 1-10 years of age, has also shown positive results.[15] The prophylaxis group reported 11 joint bleeds during the study period vs 57 joint bleeds in OD treatment group. Also, hospital visits reduced to 1 versus 9 and school absenteeism reduced to 3 versus 25 in the prophylaxis group vs OD group.[15]

Currently, cost is one of the most important aspects in Hemophilia care and the costs of factor concentrates amount to 90% of the total healthcare direct costs of hemophilia care.[16] The factor VIII concentrates available in the market are very costly and are not affordable for the general population hence, they are mostly dependent on the government for the treatment. Hence, this study is designed to assess the cost-effectiveness of the prophylactic treatment vs on-demand treatment. The prophylactic treatment option has been found to be cost-effective in many studies done in the developed countries.[16] But none such study has been done in Indian context or for any developing country. An economic evaluation done in Indian context will be able to provide an evidence about the cost-effectiveness of one of the treatment options and will support the policy makers during the decision-making process regarding upgrading the treatment modality or continue with the current one.

3. Review of Literature:

Studies for cost-effective evaluations to compare the two treatment options for Hemophilia A, i.e. Prophylaxis (PRO) and On-demand (OD) treatment, have been done in the past decade but have been restricted to developed countries only.[16] Most of these studies have been done to calculate direct costs, and report the healthcare payer perspective for its respective countries.[16] Most of the studies have been funded by industry and are likely of risk of publication bias.[16]The studies have chosen different outcome measures in the analysis including quality adjusted life years (QALYs) gained,[17][18][19][20] number of bleeds avoided,[21][22][23]and joints damaged due to arthropathy.[21]To evaluate the cost-effectiveness, the majority of the studies have chosen Markov model using the outcomes from a randomized trial or from a retrospective cohort

study.[16]The input variables used in these evaluations have been taken from secondary literature, and data from various randomized trials and other reports has been utilized.[16] Using data from randomized trials has been suggested as the best method to ensure minimum bias during the evaluation.[1624] The randomized studies done to demonstrate the effectiveness of prophylactic treatment vs on-demand treatment have matched the following factors for both treatment groups to ensure an unbiased result: (a) age of the participants in both groups, (b) severity of Hemophilia A, and (c) type of prophylaxis provided.[915] No randomized studies specific to adults in Indian context have been found in the literature.

The results of such cost-effectiveness analysis have been found to be influenced by (a) type of factor (e.g. recombinant or plasma-based factor VIII), (b) treatment efficacy of the strategy (number of bleeds occurred or avoided), (c) type of outcome measure (e.g. bleeds avoided or absence damage of joint or QALYs), and(d) time horizon used in the study.[16] The prophylactic treatment option has been reported as a cost-effective option, than the on-demand option in few countries but this observation has been reported to be highly dependent on several elements such as (a) dosing regimens, (b) cost of the factor product, (c) relative efficacy, and (d) annual background bleeding rate.[16]

A review of cost-effectiveness analysis recommends using the following methodological elements to reduce the uncertainty of the results: (a) using a life-time horizon to perceive the effects for life-time duration of a PWH, (b) using outcome measure with higher generalizability (QALYs), (c) using the inputs from multiple studies, with larger sample sizes, (d) using

standardized dosages and frequency of FRT , (e) equal discount rates for costs and outcomes, and (f) properly defining the uncertainty of the results.[16]

4. Aims and Objectives:

4.1 Aim: The study aims to produce evidence that can help to make a choice for cost-effective strategy for treatment of Hemophilia A in India. The study intends to present the healthcare payer's perspective about the costs and benefits of both PRO and OD treatment options from India, a resource limited country.

4.2 Objectives:

1) To examine the status of treatment of Hemophilia A in terms of availability of different treatment options in India
2) To compare the direct costs of different treatment modalities of Hemophilia A
3) To compare the Quality of Life (QoL) of the patients on different treatment modalities of Hemophilia A
4) To measure the cost-effectiveness of the different treatment options of Hemophilia A available in India

5. Methodology:

To evaluate the cost-effectiveness of prophylaxis (PRO) vs on-demand (OD) treatment in patient with severe hemophilia, a Markov model has been adapted which was first used by

Miners et. al in 2002.[24] The model simulates patient's clinical progression from health state 'Alive' to 'Bleeding' to 'Hospitalization' till 'Dead' (Fig. 1). A hypothetical cohort of patients under PRO and OD treatment is used in the model and the model is run for each group till all the patients attain the dead state. All individuals of the cohort start in the health state "Alive" in the first cycle. In the next cycle, the individuals move to either health state 'Bleeding' or 'Dead'. From the state of 'Bleeding', the individuals move to the state 'Hospitalization' or directly move to the state 'Dead'. From the state 'Hospitalization' they move back to the state 'Bleeding'. The Model starts at 18 years of age and runs in 1-year cycles until the age where the cohort is dead. Transition probabilities allow the progression from one health state to another. Costs and benefits are assigned to each health state to assess the cost-effectiveness.

The evaluation is done as a cost-utility analysis and the outcome measure is taken as Quality adjusted life years (QALYs) as the health-related quality of life (HR-QoL) is considered as an important outcome while comparing both the treatment options in Hemophilia A.

The model accounts for the direct costs involved in both treatment modalities which has been taken as the drug (Factor VIII) costs. The difference in costs of both the treatment options have been calculated to measure the incremental costs. For the outcome measures, the model accounts for the QALYs for the health states 'Alive', 'Bleeding' and 'Hospitalized', for both treatment options. The difference in QALYs of both treatment options have been calculated to measure the incremental benefits. The Incremental Cost-Effectiveness Ratio has also been calculated to present the costs involved to gain one health outcome, one QALY, and to answer the research question.

The data to be used to put in the model should ideally come from a randomized controlled trial (RCT) to produce unbiased results but since no RCT has been done for assessing the differences between PRO and OD treatment specific for adults in India, the data has been collected from various sources (presented in Table No. 1) to be used in the model. The Model has been created and run using Microsoft excel to represent scenarios of the two treatment modalities, OD and PRO.

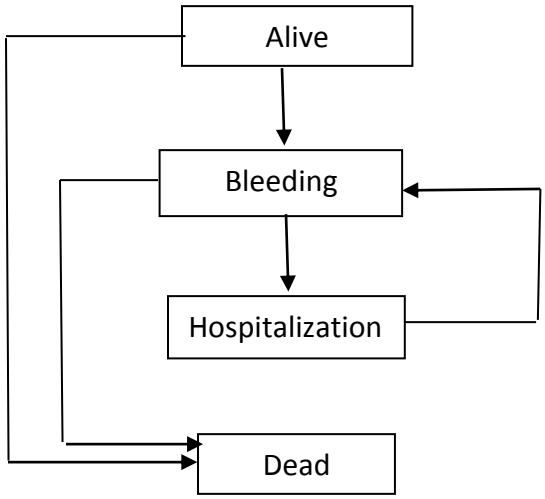

Figure 1: Markov Model presenting the health states during the lifetime of PWH

An observational study was done to obtain the retrospective data from PWH residing in India taking prophylactic treatment and on-demand treatment for treating Hemophilia A. The data was collected with the help of two tools of data collection. The variables for which data could not be collected directly from the patients, secondary sources were referred to obtain the required information.

5.1 Ethical Approval:

The Institutional Review Board (IRB) for the Protection of Human Subjects of IIHMR University, Jaipur, India (IORG0007355) was approached for the ethical approval of this study.

5.2 Data Collection

5.2.1 Target Population: Patients of Hemophilia A in India in the year 2019

5.2.2 Source Population: Patients of Hemophilia A registered with Hemophilia Federation of India (HFI) in year 2019

5.2.3 Study Population: Patients from source population with age 18 years or older, are feasible to reach and report, and who agree to participate in the study and give consent to interact.

5.2.4 Inclusion Criteria: Patients from source population with age 18 years or older, with Factor VIII deficiency level less than 1% and currently taking AHF (Anti-hemophilic factor) for treatment of the condition.

5.2.5 Sample Selection: Since Hemophilia A is an orphan genetic disorder with 15,920 PWH in India, the data was collected with the help of Hemophilia Federation of India (HFI) and its Chapters present in different cities in India. A list of Chapters under HFI was referred and Chapters with more than 50 number of registered patients were selected. Study population was identified, according to the eligibility criteria mentioned, from the list of registered patients of the Chapters agreeing to contact patients. Since the disease is of rare nature, there is unavailability of PRO treatment modality in public hospitals, the cost of the modality is very

high, hence, from the identified study population, all the PWH on PRO were considered for the study as per convenience sampling according to the eligibility criteria. A comparable age group of PWH on OD treatment was considered for the other group at a ratio of 1:2. For each PWH on PRO, 2 PWH on OD of comparable age were considered. If more than 2 PWH on OD treatment were available for 1 PWH of prophylaxis as per the above criteria, 2 PWH were randomly selected from the available OD PWH.

5.2.6 Sample Size:21 patients were considered for Prophylactic treatment group and 42 patients were considered for On-demand treatment group.

5.3 Methods of Data Collection:

Primary data and secondary data were used in the study to assess the cost-effectiveness of prophylactic treatment vs on-demand treatment option in India. Secondary data was collected from various published sources. Primary data was collected through structured questionnaires as explained in the below section.

5.3.1 Tools of data collection:

A 37-item questionnaire was developed to assess the different parameters related to health conditions, type of treatment, cost incurred in seeking the treatment etc.

For Quality of Life: EuroQoL (EQ5D) questionnaire has been adopted to assess the quality of life of the patients for the health states ‘Alive’ and ‘Hospitalized’.

The questionnaire was a self-administered tool, available in offline and online formats.

Members of HFI, Chapters and research person were available for any help required to answer any queries of the participants.

5.4 Data Analysis:

To achieve the study objectives, we plan to calculate the cost of providing prophylactic treatment vs the cost of proving on-demand treatment for a life-time horizon to PWH in India. We plan to calculate the life-time QALYs for both treatment option. Markov model enables to calculate both costs and QALYs after putting in the values of required variables in it. The collected data from both primary and secondary sources was used to produce the values for input variables of the Markov model. Table 1 gives the values of different variables used to put in the model and their source.

5.4.1 Model Inputs

Cost of the Anti-Hemophilic Factor (Factor VIII): The costs of factor VIII are required to calculate the costs of both treatment options according to their dosages. Cost of recombinant Factor VIII drug was taken from ESIC (Employees' State Insurance Corporation) drugs purchase amendment RC 140/2019.[25]The average cost of AHF for pack of 500 IU and 250 IU was considered as on date 1st July,2019.

Probabilities of death: The probability of death was required to calculate the distribution in health state 'Dead'. The cause specific mortality data for hemophilia in India was not available, hence the probability of death for the patient on on-demand treatment and PRO treatment was taken from the study of Darby et. al. measuring the death rates for both treatment modalities

in UK perspective. [26] The data for missing age groups was calculated through linear interpolation.

Bleeding Frequency: The frequency of bleeding was required to calculate the Factor VIII units consumed per year by PWH receiving OD treatment. bleeding rate was taken from the collected data for both treatment modalities.

Units of Factor consumed: The units of factor used per bleed and units used for prophylactic dose was required to calculate the Factor VIII units consumed per year by both treatment groups. The units of factor used per bleed and the weekly dosage for individuals on PRO treatment was taken from the collected data. For the case of low-dose prophylaxis, the dosage was taken as per the guidelines of WFH for prophylaxis in resource limited countires.[13]

Probability of transition into health states: Data on number of bleeds and number of hospitalizations was collected and the probabilities of entering in the respective health state was taken by calculating the Bleeding rate and Hospitalization rates for both treatment modalities.

Utility weights: To calculate the QALYs, the data on utility weights was calculated using EuroQoL (EQ-5D) for health state 'Alive' and 'Hospitalization' for individuals on on-demand patients and 'Alive' state for prophylaxis treatment.

Discount rates: Discount rates were required to include the time-value of money and costs of the both treatment in future years. Discount rates were taken as per WHO's recommendations

for cost-effectiveness analysis in healthcare.[27]The base case was evaluated with discounting rate of 5.98% as per the inflation rates in India.[28]

Table 1: Input variable values used to evaluate the base case and their sources.

Input Variable	**Input Value**	**Data Source**	**Details**
Cost of recombinant factor VIII	INR 17.5 per unit	Secondary	ESIC-Drug purchase contract-RC140/2019[25]
Bleeding per year (OD)	15	Primary	Median bleeding rate per year reported
Dosage per bleed (OD)	1129 IU	Primary	Median dosages per bleed reported
Dosage per week (PRO)	3500 IU	Primary	Median dosages per week reported
Low Dose (PRO)	15IU/kg/thric e per week	Secondary	WFH guideline on management of Hemophilia for resource limited countries[13]
Average weight of Indian Male	60kg	Secondary	Country specific nutrient requirement status[29]
Utility weight 'Alive' (OD)	0.57	Primary	Median utility from reported EQ5D
Utility weight 'Alive' (PRO)	0.7	Primary	Median utility from reported EQ5D
Utility weight 'Hospitalization	0.4	Primary	Median utility from reported EQ5D

Discount Rates	5.98%	Secondary	Inflation rates July '19[28]
Probability of bleeding (OD)	0.97	Primary	No. of respondents bleeding (OD)/Total no of respondents (OD)
Probability of hospitalization (OD)	0.56	Primary	No. of respondents hospitalized due to bleeding (OD)/No. of respondents bleeding (OD)
Probability of bleeding (PRO)	0.90	Primary	No. of respondents bleeding (PRO)/Total no of respondents (PRO)
Probability of hospitalization (PRO)	0.315	Primary	No. of respondents hospitalized due to bleeding (PRO)/No. of respondents bleeding (PRO)
Probability of dying (OD)	Age Prob. 2 0.0051 9 0.0007 19 0.0026 29 0.0058 39 0.008 49 0.0178 59 0.0392 69 0.667 79 0.133	Secondary	Darby et al.[26]

	100 1		
Probability of dying (PRO)	Age Prob. 2 0.002 9 0.0005 19 0.0011 29 0.0017 39 0.002 49 0.0058 59 0.0154 69 0.043 79 0.0917 100 1	Secondary	Darby et al.[26]

5.4.2 Key Assumptions of the model

1) The frequency of bleeding for OD PWH is same in all age groups from 18 years till death in the time horizon.
2) Recombinant factor VIII is being used as the product for treatment in both OD and PRO treatment modalities.
3) The weekly dosages of AHF for PRO, the dosage per bleed for OD, the transition probabilities for health state 'Bleeding' and 'Hospitalization', and the utility weights are same for all age groups from 18 years till death in the time horizon.

4) The utility weights for health state 'Hospitalization' for PRO patients has been assumed to be equivalent to 'Hospitalization' state for OD. And the utility for state 'Bleeding' for PRO was assumed to be same as 'Alive' due to very low bleeding frequency while on PRO as mentioned in the literature. [91514]
5) The probability of dying is same when the patient is in health state 'Alive' and 'Bleeding' as the data available to us is all cause mortality data for Hemophilia.
6) The utility weight for the health state 'Bleeding' is as per the value calculated by interpolation between other 2 health states.[30]
7) The outcome measure is independent of other physical exercises of the individuals.

5.4.3 Calculation of Costs and Benefits

Cost for on-demand treatment: The annual cost of AHF was multiplied into the proportion of individuals in health states 'Bleeding' and 'Hospitalization' for each cycle. This was done for each cycle. The sum of costs of each cycle was the total cost of the on-demand treatment option.

For one cycle the costs for On-demand treatment was calculated:

$$(\text{Proportion}_{\text{health state 'Bleeding'}} \times \text{Cost of OD}_{\text{per year}})$$

where, Cost OD per year = (Dosage per bleed × Bleeding per year) × Cost of Factor VIII per unit

Cost for prophylaxis treatment*:* The annual cost of AHF was multiplied into the proportion of individuals in health states 'Alive', 'Bleeding' and 'Hospitalization' for each cycle. The sum of costs of each cycle was the total cost of the prophylaxis treatment option.

For one cycle the costs for prophylaxis treatment was calculated:

$$(\text{Proportion}_{\text{health state 'Alive'}} \times \text{Cost of PRO}_{\text{per year}}) + (\text{Proportion}_{\text{health state 'Bleeding'}} \times \text{Cost of PRO}_{\text{per year}})$$

where, $\text{Cost of PRO}_{\text{per year}} = \text{Factor VIII Units Consumed per year} \times \text{Cost of Factor VIII per unit}$

QALYs: The QALYs were calculated by multiplying the utility weights of the health state into its respective proportion of individuals for each cycle. The sum of QALYs during each cycle was the total QALYs of the on-demand vs prophylaxis treatment option.

Proportion in health state: The proportion of each health state was calculated according to the probability of transition into respective health state.

For one cycle of one year the proportions were calculated:

1) Health State 'Alive' (A): $A_{\text{previous year}} + (0) - (A_{\text{previous year}} \times \text{Probability}_{\text{dying from alive}}) + (A_{\text{previous year}} \times \text{Probability}_{\text{bleeding}})$
2) Health State 'Bleeding' (B): $B_{\text{previous year}} + (A_{\text{previous year}} \times \text{Probability}_{\text{bleeding}}) - (B_{\text{previous year}} \times \text{Probability}_{\text{dying from bleeding}})$
3) Health State 'Hospitalization' (H): $\text{Proportion}_{\text{health state Bleeding}} \times \text{Probability}_{\text{hospitalization}}$
4) Health State 'Dead' (D): $D_{\text{previous year}} + (A_{\text{previous year}} \times \text{Probability}_{\text{dying from alive}}) + (B_{\text{previous year}} \times \text{Probability}_{\text{dying from bleeding}})$

Both costs and QALYs were discounted at a rate of 5.98% for the base case and 3% for other.

5.5 Sensitivity Analysis

One-way sensitivity analysis was done to assess the alteration in the ICER due to change in the values of one input variable. Random input values were generated according to the distribution of the variable keeping other variables constant. The model was reiterated 100 times for each variable to calculate the ICER.

Table 2: Input Variable and their distribution used for performing one-way sensitivity analysis

Input Variable	Distribution
Bleeding per year (OD)	Log Normal (1.17,0.42)
Dosage per bleed (OD)	Log Normal (3.07,0.2)
Dosage per week (PRO)	Log Normal (3.43, 0.38)
Utility weight 'Alive' (OD)	Beta (2.91,2.02)
Utility weight 'Alive' (PRO)	Beta (2.21,1.39)

6. Results:

During the study we could understand that currently on-demand treatment is provided in the public hospitals. Though it is provided free of cost, due to factors like the shortage of drug, the QoL of PWH is affected.

The results were calculated for the cost of providing the OD and PRO treatment. For the Base case, at a discount rate of 5.68%, the costs involved in providing on-demand treatment are INR42,85,032 while the costs involved in providing prophylaxis treatment are INR 5,27,74,902.

Benefits were calculated in terms of QALYs, as a measure of quality of life, for patients on OD and PRO treatment. The QALYs for prophylaxis treatment were 9.6 and 4.2 for OD treatment with an Incremental Cost Effectiveness ratio (ICER) of 90,84,163. ICER, when the treatment regimen is changed from OD to PRO and have been presented in the Table 3. This tells us that a cost of INR 90,84,163 is involved to increase the QALY by 1 unit. The ICER was also calculated at discount rate of 3%.

ICER was calculated for base case with a discount rate 5.98% and taking median values for putting in the model. Another case was calculated for low dose prophylaxis with dosage 15 IU/kg thrice per week with discount rates 5.98%. The average body weight of Indian male was taken as 60 kg to calculate the doses.[29]The results were also calculated for discount rates of 3% as suggested by WHO.[27]

The difference in quality of life (QoL) of the PWH on PRO and OD in India has not been documented till now. However, studies in many developed countries has shown improved QoL on shifting to PRO from OD treatment.[9] During this study, the patients who shifted from OD to PRO treatment during their lifetime reported the following most important changes in their life:

(a) “All seven days’ work is possible now” – 30 years, Meerut
(b) “Better joint health” & “no interruptions in work” – 25 years, Bengaluru
(c) “Healthy and active life” – 27 years, Lucknow
(d) “Drastic reduction in number of bleeds” & “more active lifestyle” – 32 years, Chandigarh
(e) “No spontaneous bleeds”, “less bleeds than before” and “positive mindset” – 27 years, Delhi

Table 3: ICER for Median values of PRO

Discount Rates	Incremental Costs (INR)	Incremental QALYs	ICER
5.98% (Base)	4,84,89,871	5.34	9084164
3%	7,81,72,855	9	8684336

Table 4: ICER for Low-dose PRO

Discount Rates	Incremental Costs (INR)	Incremental QALYs	ICER
5.98% (Base)	3,64,27,036	5.34	6824294
3%	5,87,66,896	9	6528500

6.1 Sensitivity Analysis

One-way sensitivity analysis done to evaluate the sensitivity of the model to input variables. The ICER was calculated on changing the variable values. Model was reiterated 100 times for one input variable to generate 100 ICER values. The minimum and maximum ICER were recorded and their difference was noted to assess the amount of change occurring due to the change in input variable. The results are depicted in Figure 2 showing high dependency of the results on Utility weight for 'Alive' (PRO) and the Dosage per week (PRO).

Table 5: Sensitivity analysis showing the effect of changing the input variables on ICER.

Variable	Minimum ICER	Maximum ICER	Difference

Bleeding per year (OD)	2216202	9821077	7604875
Dosage per bleed (OD)	7102793	9582151	2479358
Dosage per week (PRO)	76172	141203518	141127346
Utility Weight 'Alive' (OD)	8338566	9838184	1499618
Utility Weight 'Alive' (PRO)	-812642489	874559903	1687202392

7. Discussion:

The treatment of Hemophilia in India is provided at district level hospitals and tertiary health centers in India. In many states, specialized centers are available for the treatment in form of Hemophilia Day Care Centers (HDCC). India has extremely low usage rates of AHF products with per capita usage of 0.155 in 2017 in contrast to 9.57 in US and 0.373 in Thailand.[6]The possible causes of such low usage, even after having the highest number of PWH in India, could be OD treatment modality as compare to PRO used in the developed nations. Other contributing factors could be the shortage of clotting factor at the public hospitals and the costly nature of the drug.[10]

While HFI plays a pivotal role in providing humanitarian aid, increasing awareness about the disease and the treatment options available, not all PWH are able to access the best quality of treatment available in the country. It was found that the type of product used to treat differs at different treatment centers and across different states in India. Physiotherapy exercises have proved to be beneficial and amounts to a significant difference in the quality of life of PWH.[31] But physiotherapy consultations are not provided in all hemophilia treatment centers across

the country. Hence, a risk of confounding due to frequent change in the type of product used, access to physiotherapy and use of supporting medications is present. To do a cost effectiveness analysis for PRO vs OD treatment, it is highly recommended to use data from a randomized controlled trial to avoid such confounding factors.

In this study, 90.4% of the PWH on PRO were taking recombinant factor VIII while others were not sure of the type of products. 81% of the participants on PRO were sure of using the same product for more than 1 year of duration while others reported switching between products. 57% of the participants on PRO reported starting the prophylaxis treatment after an established joint damage (tertiary prophylaxis), 14% reported starting after onset of serial bleeding (secondary prophylaxis), 14% reported starting prior to two joint bleeds (primary prophylaxis) and were not sure of this information.

The cost-effectiveness analysis in form of a cost-utility analysis was done in this study and information from various sources was used for the evaluation. To interpret the cost-utility analysis, the incremental costs and QALYs are distributed on a Cost-Effectiveness plane (CE Plane) as shown in Fig. 2.[32] If the costs of the new treatment is higher than the old treatment, it is considered as cost-increasing; while if the costs of the new treatment is lower than old treatment, it is considered as cost-saving.[32] And if the outcome has been improved, like QALYs gained or DALYs averted, it is considered as more effective.[32] For higher cost and lower effects, it is considered 'Dominated'; for higher effects and lower costs, it is considered 'Dominant'; for higher costs and effects, Incremental cost-effectiveness ratio (ICER) has to be considered.[32] In this analysis, prophylactic treatment modality for patients with Hemophilia A has been found as

cost-increasing and more effective, as QALYs have been gained, when compared with on-demand treatment.

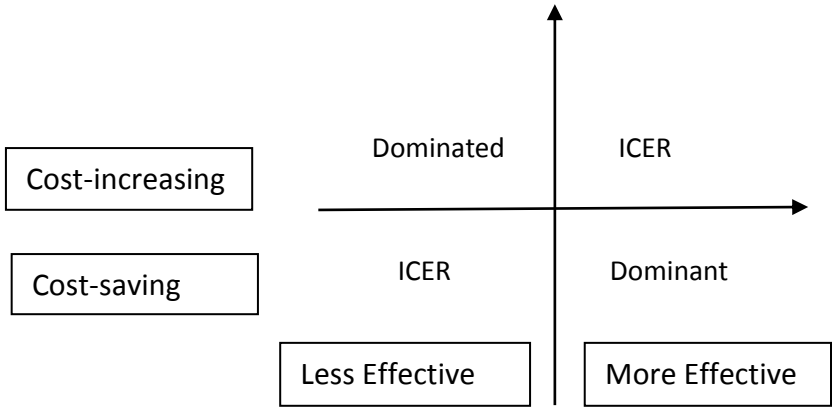

Figure 2: Cost Effectiveness Plane

Cost-utility analysis (CUA) have been done in other studies in context of different countries. CUA comparing on-demand treatment vs escalating dose prophylaxis in Canada context by Risebrough et al. (year 2003)used Markov model for a time horizon of 5 years and evaluated the ICER as Can$542,938 per QALY.[21]While other CUA done for a lifetime horizon showed the following results:

(A) Miners et al. (year 2002) using Markov Model for UK context comparing primary prophylaxis vs on-demand treatment: ICER £38,000 per QALY[24]

(B) Colombo et al. (year2010) using Markov Model for Italy context comparing:[17]

i) Primary Prophylaxis vs on-demand treatment: ICER €40,236 per QALY

ii) Secondary Prophylaxis vs on-demand treatment: ICER €40,229 per QALY

iii) "Hybrid" vs on-demand treatment: ICER €119,134 per QALY

(C) Farrugia et al. using Markov Model for UK, US and Sweden context comparing primary prophylaxis vs on-demand treatment:[19]

i) US: ICER US$68,109 per QALY

ii) UK: Cost saving

iii) Sweden: ICER SEK 484,888 per QALY

(D) Castro Jaramillo et al. (year 2013) using Markov Model for Columbia context comparing primary prophylaxis vs on-demand treatment: ICER US$91,147 per QALY using rFVIII[33]

It was difficult to compare this study to the above CUAs since this was done in context to a developing country and includes participants on any type of prophylaxis. Interpreting the results of the ICER to determine if it agreeable and acceptable depends on several factors including the prosperity of the country, the economic conditions and health priorities of the nation. Depending on the above and other affordability elements, a standard would be set by the health system of the country to consider the ICER acceptable for the country.[32] Since no cost-effectiveness analysis has been done for treatment of Hemophilia A in Indian context, it was unable to compare it to the results of any previous evaluations which were considered by the policy makers.

The results of the ICER are highly dependent on the different variables used to calculate the ICER and the data used in the model for both type of treatments. Due to unavailability of the ideal data from randomized controlled trial, we used data from different sources including

primary data collected for various variables. Due to various reasons including the smaller sample size in the collected data and the assumptions made for the calculations, the quality of the variables used cannot be considered of the highest order to evaluate the ICER. The data collected followed non-normal distribution for various variables, especially for the cost variables, hence, the median scores were chosen, and a deterministic model was created to demonstrate the ICER for base case. The ICER was highly sensitive to the time horizon, the type of AHF products used, dosage of AHF and the discount rates.

Due to the limitations of the study, it is highly possible that the ICER is underestimated in this study. Major limitations of the study include:

1) The non-availability of data from randomized controlled trail due to which data from various sources was considered to do the analysis including the primary data collected, mortality data being used from a developed country and assumptions made for various data for the evaluation.
2) The primary collection of data included limited number of participants, 21 for prophylaxis group and 42 for on-demand group which was also sensitive to recall bias. Many participants were not aware of their joint health prior to starting the treatment, which could affect their QoL scores. The participants were using either plasma-based products, or recombinant product of AHF and some were even unaware of the type of product used which could also affect the health outcome.

3) The bleeding rates were calculated using number of participants reported bleeding from the respective cohort irrespective of the number of times bleeding was experienced which could affect the health state distribution.

8. Conclusion:

In conclusion, the study suggests that low dose prophylaxis can be considered for increasing the quality of life of Hemophilia A patients in India depending upon the economic conditions of the country. It was seen that the selection of appropriate and uniform AHF product is important to determine the outcomes and costs for the analysis. Hence, providing one treatment across the nation would result in more accurate evaluation. Also, the study included more than 50% of participants on tertiary prophylaxis, estimated to be an important factor involved in reducing incremental QALYs and increasing ICER. Hence, further study would be required to measure more precise costs and QALYs for specific type of prophylaxis vs OD treatment with using same AHF products for all participants. It was observed, that until a randomized study presenting the outcomes, including QALYs, for primary, secondary, tertiary prophylaxis and on-demand treatment for all age groups including adults is not done, it is difficult to estimate the precise cost-effectiveness of the treatment.

9. References:

1. Christianson A, Howson CP, Modell B. MARCH OF DIMES. 2006.

2. Kar A, Phadnis S, Dharmarajan S, Nakade J. Epidemiology & social costs of haemophilia in India. *Indian J Med Res*. 2014;140(1):19-31. http://www.ncbi.nlm.nih.gov/pubmed/25222774. Accessed May 20, 2019.

3. Dye DE, Brameld KJ, Maxwell S, Goldblatt J, O'Leary P. The impact of single gene and chromosomal disorders on hospital admissions in an adult population. *J Community Genet*. 2011;2(2):81-90. doi:10.1007/s12687-011-0043-3

4. Christianson A, Modell B. Medical Genetics in Developing Countries. *Annu Rev Genomics Hum Genet*. 2004;5(1):219-265. doi:10.1146/annurev.genom.5.061903.175935

5. Study RF, Centre C. Report of an expert workshop held at the. 2005;(April):14-20.

6. World Federation of Hemophilia. Annual Global Survery. 2017;(October). www.wfh.org.

7. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1). doi:10.1111/j.1365-2516.2012.02909.x

8. Guelcher C, Rn-Bc H. *© National Hemophilia Foundation 2018 Nursing Working Group-Nurses' Guide to Bleeding Disorders Inhibitor Development*.; 2018. https://www.hemophilia.org/sites/default/files/document/files/Nurses-Guide-Chapter-12-Inhibitor-to-Factor-VIII-and-Factor-IX.pdf. Accessed May 20, 2019.

9. Tagliaferri A, Feola G, Molinari AC, et al. Benefits of prophylaxis versus on-demand

treatment in adolescents and adults with severe haemophilia A: the POTTER study. *Thromb Haemost*. 2015;114(07):35-45. doi:10.1160/th14-05-0407

10. Dharmarajan S, Phadnis S, Gund P, Kar A. Out-of-pocket and catastrophic expenditure on treatment of haemophilia by Indian families. *Haemophilia*. 2014;20(3):382-387. doi:10.1111/hae.12324

11. Kar A. Making haemophilia a global priority. *Lancet*. 2012;380(9838):216-217. doi:10.1016/S0140-6736(12)61214-8

12. Nolan B, Mahlangu J, Perry D, et al. Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with haemophilia A. *Haemophilia*. 2016;22(1):72-80. doi:10.1111/hae.12766

13. Makris M, Kasper C. The World Federation of Hemophilia guideline on management of haemophilia. *Haemophilia*. 2013;19(1):1-1. doi:10.1111/hae.12074

14. Sidharthan N, Sudevan R. Low Dose Prophylaxis in Hemophilia Care. *Indian J Hematol Blood Transfus*. 2019;(June). doi:10.1007/s12288-019-01147-0

15. Verma SP, Dutta TK, Mahadevan S, et al. A randomized study of very low-dose factor VIII prophylaxis in severe haemophilia - A success story from a resource limited country. *Haemophilia*. 2016;22(3):342-348. doi:10.1111/hae.12838

16. Cortesi PA, D'Angiolella LS, Lafranconi A, Micale M, Cesana G, Mantovani LG. Modern Treatments of Haemophilia: Review of Cost-Effectiveness Analyses and Future Directions. *Pharmacoeconomics*. 2018;36(3):263-284. doi:10.1007/s40273-017-0588-z

17. Colombo GL, di Matteo S, Elisa Mancuso M, Santagostino E. Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. *Clin Outcomes Res*. 2011;3(1):55-61. doi:10.2147/CEOR.S16670

18. Miners A. Revisiting the cost-effectiveness of primary prophylaxis with clotting factor for the treatment of severe haemophilia A. *Haemophilia*. 2009;15(4):881-887. doi:10.1111/j.1365-2516.2009.02019.x

19. Farrugia A, Cassar J, Kimber MC, et al. Treatment for life for severe haemophilia A- A cost-utility model for prophylaxis vs. on-demand treatment. *Haemophilia*. 2013;19(4):228-238. doi:10.1111/hae.12121

20. Coppola A, D'Ausilio A, Aiello A, et al. Cost-effectiveness analysis of late prophylaxis vs. on-demand treatment for severe haemophilia A in Italy. *Haemophilia*. 2017;23(3):422-429. doi:10.1111/hae.13185

21. Risebrough N, Oh P, Blanchette V, Curtin J, Hitzler J, Feldman BM. Cost-utility analysis of Canadian tailored prophylaxis, primary prophylaxis and on-demand therapy in young children with severe haemophilia A. *Haemophilia*. 2008;14(4):743-752. doi:10.1111/j.1365-2516.2008.01664.x

22. Daliri AAK, Haghparast H, Mamikhani J. Cost-effectiveness of prophylaxis against on-demand treatment in boys with severe hemophilia A in Iran. *Int J Technol Assess Health Care*. 2009;25(4):584-587. doi:10.1017/S0266462309990420

23. Gringeri A, Lundin B, Von Mackensen S, et al. A randomized clinical trial of prophylaxis in

children with hemophilia A (the ESPRIT study). *J Thromb Haemost*. 2011;9(4):700-710. doi:10.1111/j.1538-7836.2011.04214.x

24. Miners AH, Sabin CA, Tolley KH, Lee CA. Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia. *Pharmacoeconomics*. 2002;20(11):759-774. doi:10.2165/00019053-200220110-00005

25. cost of factor VIII esic.pdf.

26. Darby SC, Kan SW, Spooner RJ, et al. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood*. 2007;110(3):815-825. doi:10.1182/blood-2006-10-050435

27. WHO | Generalized Cost-Effectiveness Analysis. *WHO*. 2014. https://www.who.int/choice/cost-effectiveness/generalized/en/. Accessed August 30, 2019.

28. Data S, Consumer AA, Index P, et al. Feb Apr Aug Sep Oct Nov Dec Average. 2017.

29. Nair KPM, Augustine LF. Country-specific nutrient requirements & recommended dietary allowances for Indians: Current status & future directions. *Indian J Med Res*. 2018;148(5):522. doi:10.4103/IJMR.IJMR_1762_18

30. Lamers LM. The Transformation of Utilities for Health States Worse Than Death. *Med Care*. 2007;45(3):238-244. doi:10.1097/01.mlr.0000252166.76255.68

31. Kar A, Mirkazemi R, Singh P, et al. Disability in Indian patients with haemophilia.

Haemophilia. 2007;13(4):398-404. doi:10.1111/j.1365-2516.2007.01483.x

32. Cohen DJ, Reynolds MR. Interpreting the results of cost-effectiveness studies. *J Am Coll Cardiol*. 2008;52(25):2119-2126. doi:10.1016/j.jacc.2008.09.018

33. Castro Jaramillo HE, Moreno Viscaya M, Mejia AE. COST-UTILITY ANALYSIS OF PRIMARY PROPHYLAXIS, COMPARED WITH ON-DEMAND TREATMENT, FOR PATIENTS WITH SEVERE HEMOPHILIA TYPE A IN COLOMBIA. *Int J Technol Assess Health Care*. 2016;32(5):337-347. doi:10.1017/S0266462316000544

10. Annexures

Annexure 1

Base Case at discount rates 5.98% with Median input values

Model type	Start age	Time horizon	Study perspective
Deterministic	18yr	Life time	Healthcare payer perspective

In INR	Costs	QALYs	Incremental Costs	QALYs	ICER
Prophylaxis	52774902.47	9.62452	48489870.53	5.337846382	**9084163.73**
On-Demand	4285032	4.286673			
In dollars					
Prophylaxis	736051.6384	9.62452	676288.2919	5.337846382	**126696.844**
On-demand	59763.3465	4.286673			

Case at discount rates 3%

Model type	Start age	Time horizon	Study perspective
Deterministic	18yr	Life time	Healthcare payer perspective

In INR	Costs	QALYs	Incremental Costs	QALYs	ICER
Prophylaxis	84901073.47	15.39916	78172855.16	9.001592956	**8684335.71**
On-Demand	6728218	6.397567			
In dollars					
Prophylaxis	1184115.39	15.39916	1090276.92	9.001592956	**121120.442**
On-demand	93838.47009	6.397567			

Annexure 2

Low-dose Prophylaxis Case at discount rates 5.98%

Model type	Start age	Time horizon	Study perspective
Deterministic	18yr	Life time	Healthcare payer perspective

		Costs	QALYs	Incremental Costs	Incremental QALYs	Incremental ICER
In INR	Prophylaxis	40712067.62	9.62452	36427035.68	5.337846382	6824294.49
	On-Demand	4285032	4.286673			
In dollars	Prophylaxis	567811.2639	9.62452	508047.9174	5.337846382	95178.4448
	On-demand	59763.3465	4.286673			

Case at discount rate 3%

Model type	Start age	Time horizon	Study perspective
Deterministic	18yr	Life time	Healthcare payer perspective

		Costs	QALYs	Incremental Costs	Incremental QALYs	Incremental ICER
In INR	Prophylaxis	65495113.82	15.39916	58766895.51	9.001592956	6528499.54
	On-Demand	6728218	6.397567			
In dollars	Prophylaxis	913460.4437	15.39916	819621.9737	9.001592956	91052.9923
	On-demand	93838.47009	6.397567			

Annexure 3

Institutional Review Board Certificate

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Institutional Review Board (IRB) for the Protection of Human Subjects
IORG0007355 OMB No. 0990-0279

Format for Approval

	Serial No. of Institutional Review Board/ Approval Number	August 2019	1
1	Project Title: Cost effectiveness analysis of prophylactic vs on-demand treatment for Hemophilia A		
2	Name of Faculty In-charge/ Ph D Scholar	Prerika	
3	Date of Submission to the IRB	09082019	
4	Date of Submission to the Agency	NA	
5	Review Category of the Proposal		
	Expedited Review		
	Full Review	√	
	Exemption from Review		
6	Date of Review	17082019	
7	Reviewer's Name	Dr D K Mangal, Dr Anoop Khanna, Dr Nutan Prabha Jain	
8	Reviewer's Feedback (Please tick the following, if you are satisfied)		
8.1	Respect for person	√	
8.2	Fair subject selection	√	
8.3	Informed consent	√	
8.4	Maintaining privacy	√	
8.5	Maintaining confidentiality	√	
9	Final Comment		
	Approved without suggestions		
	Approved with suggestions	√	
	Sent back for revision and re-submission		
	Not approved		
10	Suggestions of IRB have been incorporated up to the satisfaction of the members. Approved.	Signature	

Annexure 4

Informed Consent

Hello, my name is Prerika and I am a master's candidate at the Johns Hopkins School of Public Health, USA-IIHMR, India. I am carrying out a study on the "Cost effectiveness analysis of prophylactic vs on-demand treatment for Hemophilia A" in India. I invite you to be part of this study.

You are one of more than 15,920 persons with Hemophilia residing in India who have been selected for this study. You are being invited to take part in this study because there are different treatment modalities that are available in India for Hemophilia care. Therefore, I am interested in learning about the status and process of treatment available to you and compare the different treatment modalities for clinical outcomes, quality of life and related costs. Therefore, I will ask you about your general health related information through this questionnaire. It would take about 15-20 minutes of your time. If you accept to participate, you will be asked to share information about your health condition, quality of life, how you avail various treatment modalities and the costs related to it.

The interview will be administered in a setting that you deem comfortable. Nothing of what we discuss will be used for any purposes other than those for this research work. No one else will have access to the recorded information. If you do not wish to answer any of the questions during the interview, you may say so and/or may move on to the next question or stop the interview.

By participating in the study, you shall be contributing towards learnings of economic aspects of treatment of Hemophilia and shall be taking an active role in your own health advancement.

Participating in the study, you might experience discomfort in narrating the not so good experience of your life. I assure you, the confidentiality and anonymity of the participants shall be maintained throughout the study. The responses received will be kept in lock and password protected accounts. The

information shall be used for research purposes only. An individual information shall not be used, rather a complied data analysis shall be done so that nobody is able to know the identity.

Your decision to participate in the study is voluntary. Choosing not to participate in the research will not affect your situation in any way. You can withdraw from the interview at any time or you can also inform me later if you decide that your responses shall not be included in this study. The choice that you make will have no bearing on any of your relationships to public and private organizations. You may change your mind later and stop participating even if you agreed earlier. If any part of this information sheet remains unclear, you can contact HFI or me directly anytime via email. I will not be sharing information about you or your responses with anyone. It will be ensured that nothing recorded will allow the tracing of your identity. The information that I collect from this work will be kept private and secure. You are free to contact me directly to know the results of the study, which I shall also share with HFI and will be accessible to you.

If you have any questions, you can ask them now or later. If you wish to ask questions later, you may contact me at:

Dr. Prerika

Email: prerika.nehra@yahoo.com

May I start interaction with you?

- ☐ YES
- ☐ NO

If Yes,

Name of the Respondent: _____

Signature with Date: _____

Mobile No.: _____

Annexure 5

Questionnaire

Please click on the below link for the tools used for collecting data

1) Questionnaire

   https://drive.google.com/file/d/1oO6VDFpgT-5WJZlYQIzI8F7x09PjSFYS/view?usp=sharing

2) EQ5D for Quality of Life

   https://drive.google.com/file/d/1TXbkNTkMv1loZTeHw8I99uWg2Z_tsb11/view?usp=sharing

Annexure 6

Markov Model& Calculations

Please click on the below link for the model prepared in excel and its calculations

1) Base Case at discount rates 5.98%

   https://drive.google.com/file/d/12aPhpHlmtUiAQD3n_RpEDqfIphSDX0eM/view?usp=sharing

2) Case at discount rates 3%

   https://drive.google.com/file/d/1WVYTWC-Q0fh5zSJ3Fed-8R1m2oXjDfCP/view?usp=sharing

3) Low-dose prophylaxis case at discount rate 5.98%

   https://drive.google.com/file/d/1b3bjq0oXgtoDY_EGo6-bMn2qD0nTcXr-/view?usp=sharing

4) Low-dose prophylaxis case at discount rate 3%

   https://drive.google.com/file/d/1aGugtLghxrPiUi0yKCTfGU4pDSEtUHaR/view?usp=sharing