Health Technology Assessment of Point of Care Test Kit for Hemophilia A and Von Willebrand Disease (VWD) Screening developed at ICMR NIIH

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Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

1.1 Background and rationale

Bleeding disorders: Hemophilia and Von Willebrand disease:

Globally 1 in 1000 persons are reportedly affected by bleeding disorders (1). Hemophilia and Von Willebrand disease are most prevalent among hereditary bleeding disorders. Hemophilia is an X-linked congenital disorder, occurring due to the pathogenic variants in the coagulation factor VIII gene or the factor IX gene, resulting in the deficient synthesis of coagulation factor VIII (hemophilia A) or IX (hemophilia B) respectively, presenting as hemorrhagic tendencies in the patients. Based on the levels of clotting factor, patients are classified as having severe (<1%), moderate (1%-5%), and mild (5%-40%) disorders. The condition is typically transmitted through asymptomatic, heterozygous females to the male child (2). Approximately one-third of cases arise from a spontaneous mutation (3). The expected number of males with hemophilia worldwide is 1,125,000, the majority of whom are undiagnosed, including an estimated 418,000 males with severe hemophilia (1). The prevalence of hemophilia is commonly reported as one in 5000 in the male population and one in 10,000 overall; the global survey results show the prevalence of hemophilia A is about 11.2 cases per 100,000 men and boys in all ethnic groups (12). Hemophilia A is estimated to account for 80%-85% of all hemophilia cases (4). India has an anticipated 1,20,000 severe Hemophilia A patients with an addition of 1,500 new cases each year. However, the cases registered with Hemophilia Federation India (HFI) are only around 27,000. As per guta et,al 2005, out of 966 North Indian patients diagnosed to have inherited bleeding disorders, hemophilia A was the most common and was seen in 410 (42.4%) of the patients (15).

Von Willebrand disease (VWD) is an autosomal dominant trait affecting both sexes. It is characterized by defects in the concentration, structure, or function of Von Willebrand factor (VWF), a glycoprotein that acts as a carrier protein for factor VIII (FVIII) and facilitates platelet adhesion at vascular injury sites. It has 3 main types: Type 1 is characterized by partial quantitative VWF deficiency, resulting in a mild to moderate bleeding phenotype, whereas Type 3, the most severe form of VWD, results from near-complete absence of VWF. Type 2 VWD represents a group of disease phenotypes resulting from qualitative defects in VWF, affecting the formation of multimers (types 2A and 2B), platelet adhesion (type 2M), or FVIII binding (type 2N) (5). The most common subtype is identified as type 3 followed by types 1 and 2 (6). It is estimated that around 1% of the general population is affected by Von Willebrand Disease (4), i.e. expected VWD should be approx. 1 crore (135 crores – India's population) in India. As per jain et,al 2021, Among the 200 women with HMB, 12.5% (25 women) were diagnosed with von Willebrand disease (vWD). Type III vWD was the most common subtype, affecting 60% of these women. Type II vWD was found in 28%, and Type I vWD in 12%. Within Type II vWD, Type IIN was the predominant subtype (71%), while Type IIB was absent (14)

Table 1: Current estimates of burden of disease in India from Hemophilia Registry (2022)

State Name	Total Population (Projected 2020)	Prevalence	Identified as per NHR	Diagnosis %
Uttar Pradesh*	237882725	24859	2403	9.67
Bihar	124799926	13042	502	3.85
Maharashtra	123144223	12869	4693	36.47
West Bengal	99609303	10409	1281	12.31
Madhya Pradesh	85358965	8920	972	10.90
Rajasthan	81032689	8468	969	11.44
Tamil Nadu	77841267	8134	2459	30.23
Karnataka	67562686	7060	2859	40.49
Gujarat*	63872399	6675	2195	32.89
Andhra Pradesh*	53903393	5633	1435	25.48
Odisha	46356334	4844	572	11.81
Jharkhand	38593948	4033	376	9.32
Telangana*	38510982	4024	1221	30.34
Kerala	35699443	3731	1896	50.82
Assam	35607039	3721	356	9.57
Punjab*	30141373	3150	163	5.17
Chhattisgarh	29436231	3076	80	2.60
Haryana*	28204692	2947	430	14.59
Delhi	18710922	1955	782	39.99
Jammu Kashmir	13606320	1422	159	11.18
Uttarakhand	11250858	1176	211	17.95
Himachal Pradesh*	7451955	779	88	11.30
Tripura	4169794	436	51	11.70
Meghalaya	3366710	352	20	5.68
Manipur	3091545	323	55	17.02
Nagaland	2249695	235	0	
Goa*	1586250	166	53	31.97
Arunachal Pradesh	1570458	164	0	
Puducherry	1413542	148	282	190.91
Mizoram	1239244	130	0	
Chandigarh*	1158473	121	640	528.66
Sikkim	690251	72	0	
Dadra & Nagar Haveli and Daman & Diu*	615724	64	0	
A & N Islands*	417036	44	0	
Ladakh	289023	30	0	
Lakshadweep	73183	8	0	
	1,37,05,08,600	**143218**	**27203**	**18.99**

Source: National Hemophilia Registry for India

1.2 Pathophysiology and Complications:

Depending on the level of clotting factor in hemophilia patients the severity of bleeding varies. In the case of mild hemophilia excessive bleeding occurs only after major trauma or surgery, while patients with moderate and severe condition suffer from spontaneous bleeding in joints or soft tissue, mucosal bleeding, easy bruising, and hematoma. The bleeding in joints particularly in ankles, knees, and elbows, referred to as hemarthrosis is most common among severe patients, occurring as often as 20-30 times a year. This causes the joints to damage resulting in synovitis and over time leading to hemophilic arthropathy. These patients are also at risk of gastrointestinal or intracranial bleeding which is life-threatening (3). Patients

with VWD most often experience bleeding from mucosal tracts such as epistaxis, menorrhagia, and gastrointestinal bleeding (7). In females with VWD menorrhagia is the most common bleeding symptom affecting more than 70% (8). In type 3 VWD, associated with FVIII deficiency, soft tissue bleeding such as hemarthrosis and postoperative hemorrhages is frequent (8). In many cases, patients with hemophilia are misdiagnosed and treated without testing their coagulation ability. In a study of patients with severe hemophilia, 60% were associated with physical disability thus negatively influencing their productivity and quality of life. Lack of adequate facilities results in high rates of underdiagnoses and incorrect treatment, both of which strongly influence the quality of life and lifespan of patients with hemophilia (8). A rapid and accurate diagnosis is critical to initiate early life-saving treatment for these conditions.

1.3 Diagnosis and Treatment in India:

In India, the disease largely remains underdiagnosed due to a lack of awareness about the disease, the paucity of diagnostic facilities, and the high cost of tests. The diagnosis of both hemophilia A and VWD currently necessitates a series of expensive specialized laboratory tests which are time consuming, needs technical expertise, sophisticated instruments, costly reagents and require fresh blood samples. Initial screening focuses on evaluating proper blood clotting through routine laboratory analysis which includes platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), the international normalized ratio (INR), and bleeding time. If clotting is impaired, factor assays are conducted to pinpoint the cause of the bleeding disorder. The execution of factor assays mandates a semi- or fully automated coagulometer, alongside costly reagents such as FVIII or FIX and deficient plasma of FVIII or FIX, in addition to other local reagents. In the case of quantitative variants of VWD (type 1 and 3), their diagnosis typically relies on techniques like ELISA or other immunological assays in a fully automated coagulometer. In many laboratories, there are no facilities to diagnose VWD, and patients are often misdiagnosed with hemophilia A. The expenses associated with these tests span between Rs. 2000 to 9000 across various laboratory setups (9). There are only a few comprehensive diagnostic centers in our countries. In many of the district hospitals and even medical colleges coagulation screening facilities are not available which impact the detection of new hemophilia cases (10). In the past few years the Hemophilia Federation of India (HFI) has developed more than 90 chapters across the country to provide comprehensive care for patients with Hemophilia located in government hospitals and few run by private charitable organizations (11). As per the experts in India there are about 180 Hemophilia Treatment centers. In terms of diagnostic facilities, around 70 laboratories in the public facilities are equipped to undertake basic screening tests of PT and APTT. Out of these, around 20 are also doing factor assays and inhibitor screening. There are only 2- 3 highly advanced laboratories in the country also doing molecular diagnosis of hemophilia and other rare bleeding disorders; one in ICMR NIIH KEM Mumbai and the other in CMC Vellore.

The treatment of bleeding events follows the replacement of the deficient coagulation factor in the blood. The replacement therapy is administered either in the occurrence of a bleeding event on-demand or prophylactically in the absence of bleeding. The products used to treat hemorrhagic episodes with replacement therapy are fresh frozen plasma, cryoprecipitate, or clotting factor. Recombinant-derived Factor VIII and IX concentrates with extended half-life are available which prevent the risk of viral transmission. The treatment of von Willebrand disease consists of desmopressin (DDAVP) or cryoprecipitate. In case of hemophilia clotting factor concentrate is the most preferred treatment. However, the associated high cost places it out of reach of majority of patients. As the management of hemophilia requires life-long replacement for coagulation proteins, the development of inhibitors that

neutralize the replacement proteins (clotting factors) is a major challenge for treatment. The treatment cost per bleeding episode at primary health centre may range between Rs. 20,000 to 30,000. For moderate cases the prophylactic treatment for a 20kg child is Rs. 3 lakhs per year. In case of patients with higher complications such as intracranial bleeding the treatment is even costlier. In India, the economic conditions of PWH drive treatment decisions, and only a few patients have access to factor replacement therapy(10)(6)(3).

Table 2: Interpretation for screening test

Possible diagnosis	PT	APTT	Platelet count
Normal	Normal	Normal	Normal
Hemophilia A or B	Normal	Prolonged[a]	Normal
VWD	Normal	Normal or prolonged[a]	Normal or reduced
Platelet defect	Normal	Normal	Normal or reduced

Abbreviations: APTT, activated partial thromboplastin time; PT, prothrombin time; VWD, von Willebrand disease.

[a]The same pattern can occur in the presence of FXI, FXII, prekallikrein, or high molecular weight kininogen deficiencies.

Source: WFH Guidelines for the Management of Hemophilia, 3rd edition (4)

1.4 POC testing for Hemophilia A and Von Willebrand Disease

The ICMR-National Institute of Immunohaematology, Mumbai developed a lateral flow immunoassay (LFIAs) based point of care (POC) testing for hemophilia A and Von Willebrand disease. A “point of care” test is an investigation done at the time of consultation with the immediate availability of results to make immediate decisions about patient care. These POC test kit for hemophilia and Von Willebrand disease provide a rapid and accurate diagnosis for both the diseases without requiring any expensive screening or assay for the patients. The POC testing technology has been transferred for large scale manufacturing to Bhat Bio-Tech India pvt. Ltd. The kit is the first POC test in the world for specific diagnosis of any common bleeding disorder. The introduction of these POC test kits at the primary health care level can enable rapid and accurate diagnosis which will allow the right treatment for the patients. The kit allows simultaneous detection of FVIII:Ag and VWF:Ag from blood plasma without the need of any technical expertise and at quite reduced amount of sample compared to known techniques. Even though the kit may not provide confirmatory and quantitative information, it provides a means for differential screening for patients with hemophilia A and VWD. The available of this information at the PHC level is critical to initiate appropriate treatment and referral for the patients that can significantly influence the quality of life of patients with hemophilia.

Novelty/Innovation:

A groundbreaking development has arisen from the ICMR-National Institute of Immunohaematology in Mumbai – a straightforward, rapid, and cost-effective diagnostic kit catering to Hemophilia A and VWD. Remarkably, this marks the world's first instance of such a kit. The kit employs a lateral flow immunoassay (LFIA) for testing, enabling its use at Primary Health Centers (PHCs) without the need for specialized expertise. The proposed kit does not need any technical expertise or equipment and result can be read in 10 min after application of plasma or whole blood.

ICMR has successfully transferred this technology to Bhat Bio-Tech India (p) Ltd. (BBI) in Bangalore for the purpose of commercializing these kits. With the manufacturing license from the DCGI secured, the kit is primed for market introduction. Notably, the projected cost of the kits stands at Rs. 450. Thus, this innovative kit is poised to revolutionize the diagnostic landscape for bleeding disorders, not just within the country but also across numerous other developing nations grappling with inadequate or substandard diagnostic facilities. The study is structured to answer the policy question put forward by the Ministry to estimate the cost per test of the POC test kit for diagnosis of HA and VWD.

Figure 1: POC test kit for Hemophilia A and Von Willebrand Disease

Validation of the kit:

The kits were subjected to validation testing during the research and development phase with 300 samples were screened which encompassed individuals with normal conditions, patients with a history of bleeding, and other relevant cases. The screened patients included 137 with Hemophilia A (severe + moderate <5% F VIII) and 53 with VWD (severe <5% VWF). Before market release, an independent validation was done using various samples across five different centres - SGPGI, Lucknow; PGIMER, Chandigarh; St. John’s Hospital, Bangalore; AIIMS, New Delhi and NRS Medical College, Kolkata. The Stability study for the kit showed the kit is stable for 18 months at 4 degrees.

Table 3: Centre specific validation of POC test kit

Sr. No	CENTRES	No. of samples	Sensitivity	Specificity
A	**Internal Validation Report at R& D**			
1	ICMR-NIIH, Mumbai – **Hemophilia A (mean)**	300	96.23%	98.54%
	ICMR-NIIH, Mumbai – **VWD (mean)**		98.49%	99.32%
B	**External Independent Validation Report by 5 Centres:**			
	Overall Validation by 5 centres – **Hemophilia A (<5%)**	73	100%	98%
	Overall Validation by 5 centres – **VWD (<5%)**		100%	99%

Source: Reports on Validation from ICMR-NIIH, Mumbai

Chapter 2: Objective and Methodology

2.1 Objectives:

1. To estimate cost per test of the Point of Care test kit for diagnosis of Hemophilia A and Von Willebrand Disease.
2. To conduct budget impact analysis for the standard of care and POC test kit to detect patients with Hemophilia A and VWD at the public health facilities.

2.2 Methodology:

The present study will identify the cost per test for the POC test kit. The cost will be estimated for testing all individuals presenting with symptoms and signs of hemophilia A and Von Willebrand disease at public health facilities. As the disease is not endemic or prevalent in a specific population group, hence, the estimated proportion of entire population within the 0-40 age group will be considered. The cost per test will be identified for this population. The study will be undertaken from Health systems' perspective.

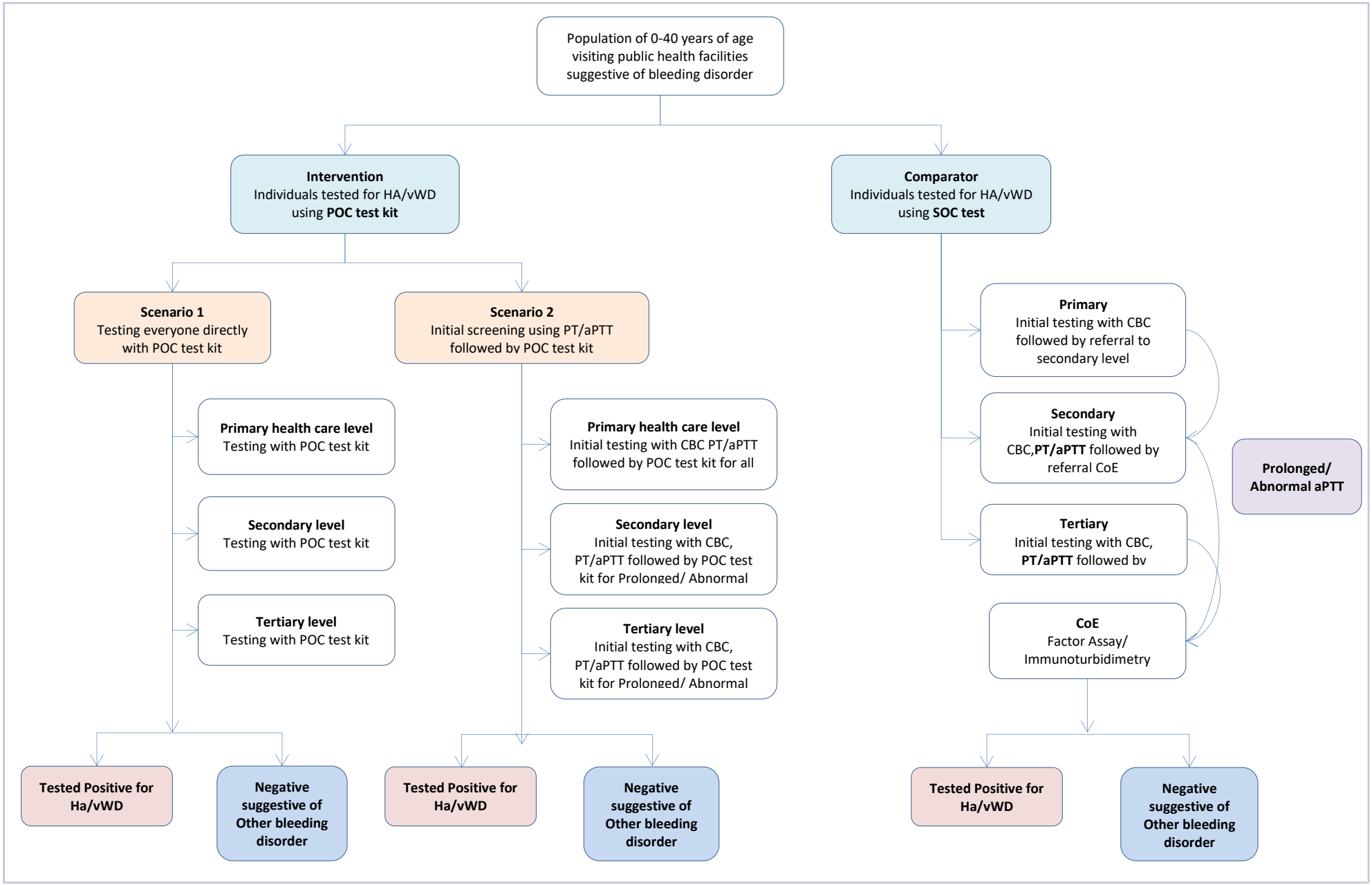
2.2.1 PICOT

Table 4: PICOT

Population	Cohort of individuals of 0-40 years of age presenting to public health facilities with symptoms suggestive of Hemophilia A and Von Willebrand disease (bleeding disorders)
Intervention	HA and VWD screening with POC test kit ➢ Scenario 1: Testing everyone directly with POC test kit ➢ Scenario 2: Initial screening using PT/aPTT followed by POC test kit
Comparator	Initial screening with PT/APTT/bleeding time, platelet count etc. and if Aptt abnormal, confirmatory factor assay and ELISA for VWD.
Outcome	➢ Cost per test for Intervention and Comparator ➢ Cost per case detected for Intervention and Comparator ➢ Number of cases detected for Intervention and Comparator ➢ Additional number of cases detected by Intervention as compared to Comparator ➢ Budget Impact Assessment
Perspective	Health System Perspective

2.2.2 Care Pathway:

Figure 2: Care-pathway for testing Hemophilia A and Von Willebrand disease using SOC and POC test



When a patient exhibiting symptoms suggestive of a bleeding disorder presents at a healthcare facility, depending on their condition's severity, basic investigations are done like CBC, PT, Aptt and they may receive initial basic treatment. The individual will be recommended for further evaluation at a higher level advanced medical facility to establish a definitive diagnosis.

Discussions with experts have revealed that Factor Assays are available at very limited public health facilities in India such as Centers of Excellence. These assays are not even uniformly available in Tertiary medical colleges in India limited access to confirmatory diagnosis. In states like Maharashtra where the lab investigations are outsourced through public private partnership these tests fall under advance category of tests making its access possible at tertiary level of care .But such examples in India are very few and are not generalized hence limiting its consideration in our analysis.

The intervention arm has two scenarios. In scenario one, all the individuals with bleeding complaints suspected on Hemophilia A/ vWD visiting primary, secondary, and tertiary care are tested with the point-of-care test. In scenario two, the individuals with bleeding complaints are initially tested for bleeding disorder using CBC/PT/aPTT as per the availability of test at the facility followed by the point-of-care test kit.

In the comparator arm, at the primary level, the individuals presenting bleeding symptoms are tested with CBC. As PT/aPTT test is absent at the primary level healthcare facilities, these patients are referred to next higher levels of care (secondary level of care). For the secondary level (along with a referral from the primary level facility) and tertiary level, the initial screening is undertaken with PT/aPTT test. The individuals with normal PT and prolonged/abnormal aPTT undergo factor assay for Hemophilia A and Immunoturbidimetry for vWD at Center of Excellence healthcare facilities to identify and confirm the presence of Hemophilia A and vWD.

2.2.3 Cost Overview:

a) **Calculation of cost of comparator:**

This would include an assessment of the cost of diagnosis for HA and VWD in terms of conventionally diagnosed cases as part of routine care. Primary health system costing was undertaken at ICMR NIIH, Mumbai. The costing was undertaken through Health system perspective with a focus on public health facilities.

The primary health system costing include bottom up approach to estimate cost of testing for Hemophilia A/vWD. Cost Centres Identified: Patient registration room, Sample collection room and Haemostasis and Thrombosis Lab. The cost and quantity of actual utilization of input resources at these cost centres was collected.

Input resources: Human Resource, Infrastructure, Furniture, Lab equipment, Lab reagent, Consumables, Stationary and Overhead. The cost of capital resources (Furniture and Lab equipment) was annualized for the reference year of the study. The cost of common resources was apportioned (HR and furniture at sample collection room).

b) Calculation of cost of the intervention:

The comprehensive cost analysis of the intervention encompasses two major components this includes the health system cost and the cost of the consumable or kit. The health system cost will be obtained from secondary data source of National Health System Cost Database for India (NHSCD). The cost of the consumable or the kit was obtained from IndiaMart.

Examination of the Cost Implications of Enhanced Healthcare Utilization due to Expanded Coverage: The hypothesis assumes that broader coverage of screening tests is likely to result in the identification of a greater number of early-stage Hemophilia A (HA) and Von Willebrand Disease (VWD) cases, as opposed to cases being identified during later stages.

2.2.4 Estimation of Effect:

The effect parameters in terms of population estimate, prevalence, sensitivity of tests, specificity of tests, coverage proportions are obtained from secondary literature review. Population cohort for 0-40 years of age was obtained from the population projection report for the year 2021. The proportion of utilization at public health facility was obtained from the Health in India report of NSS 75th round (2017-18). The population suggestive of bleeding disorder was estimated based on the prevalence. The population cohort for the analysis was estimated based on these parameters.

Based on the proportionate utilization of services at primary, secondary and tertiary level of care the population at each level was estimated. For POC test the number of test were estimated based on the population at each level as the tests were conducted at facility level. In terms of SOC test the total test at primary and secondary level for PT/aPTT were estimated. The total test for diagnosed/detected of hemophilia A and vWD will include the test conducted at Center of Excellence (CoE) healthcare facilities. The total additional cases tested using the POC test as compared to the SOC test was estimated.

Table 5: Effect and Cost Parameter

Parameter Description	Values	Lowest	Highest	Source
Population/Prevalence				
Eligible Population Size (0-40 years)	285945	257350	314539	16
Coverage of Healthcare services at Public Hospital	0.30	0.27	0.33	17
Prevalence of Bleeding disorder	0.001	0.0009	0.0011	1
Prevalence of Hemophilia A (HA)	0.0001	0.00009	0.00011	12
Prevalence of von Willebrand Disease (vWD)	0.01	0.009	0.011	14
Proportion of HA among bleeding disorder	0.53574	0.48216	0.58931	18, 19, 20
Proportion of vWD among bleeding disorder	0.07081	0.06373	0.07789	18, 19, 20

Proportion of bleeding disorder individuals getting normal PT and Prolonged/Abnormal aPTT	0.67735	0.60962	0.74509	18, 19, 20
Primary	0.70	0.63	0.77	21, 22
Secondary	0.10	0.09	0.11	21, 22
Tertiary	0.20	0.18	0.22	21, 22
Referral from lower level facility to higher facility	0.75	0.675	0.825	23, 24
Discount rate	0.03	0.027	0.033	25
Sensitivity and Specificity of tests				
Sensitivity of Hemophilia A Test kit	0.98115	0.883035	1.0000	Table 3
Specificity of Hemophilia A Test kit	0.9827	0.88443	1.0000	Table 3
Sensitivity of vWD Test kit	0.99245	0.893205	1.0000	Table 3
Specificity of vWD Test kit	0.9916	0.89244	1.0000	Table 3
Sensitivity of aPTT	0.9900	0.8910	1.0000	26, 27
Specificity of aPTT	0.8300	0.7470	0.9130	26, 27
Sensitivity of Factor assay (clot based one stage) for HA	0.9000	0.8100	0.9900	28
Specificity of Factor assay (clot based one stage) for HA	0.9000	0.8100	0.9900	28
Sensitivity of Immunoturbidimetry for vWD	0.9470	0.8523	1.0000	29, 30
Specificity of Immunoturbidimetry for vWD	0.8000	0.7200	0.8800	29, 30
Cost for Standard of Care test and POC test kit				
HSC Hemophilia test Primary Level- HR, Capital and Other Cost	58.71	29.3574	88.07219	31
HSC Hemophilia test Secondary Level- HR, Capital and Other Cost	198.54	99.2715	297.8145	31
HSC Hemophilia test Tertiary Level- HR, Capital and Other Cost	516.69	258.3451	775.0353	31
Cost of Testing PT/aPTT	200.00	100	300	*Price from public health system*

Health system cost for Standard of Care for screening and confirmation factor assay of Hemophilia A/vWD	6646.17701	3323.08850	9969.26551	*Primary health system costing (Table 6)*
Cost of Hemophilia A/vWD Kit (Rs. 200 + Rs. 250)	450.00	225.00	675.00	32

2.2.5 Budget Impact Analysis:

The budget for the hemophilia A and Von Willebrand disease testing using the POC test kit and SOC test was estimated based on the total health system cost for conducting the test. The budget was estimated for the population cohort of 285945 which included individuals of 0-40 years of age presenting at public health facility with symptoms suggestive of Hemophilia A and Von Willebrand disease. The total health system cost for both POC test kit and SOC was estimated for varied population coverage. The budget impact in terms of total cost saving with the use of POC test kit was also estimated.

2.2.6 Sensitivity Analysis:

The sensitivity analysis was undertaken to identify the robustness of the analysis. The parameter uncertainties that could influence the cost per test were evaluated by one-way sensitivity analysis (OWSA) and presented in a tornado diagram.

The sensitivity analysis was undertaken of the unit cost of SOC for testing HA/VWD at tertiary level obtained through primary health system costing. The input costs were varied 50% above and below. The effect of this variation on the unit cost was seen.

The sensitivity analysis of the cost per test for the POC test kit was undertaken. The parameter values were varied with defined range to assess their impact in variation the results. The input parameters for cost were varied between 50% above and below and for probabilities the variation was 10% above and below. The effect of this variation on the cost per test was seen.

Chapter 3: Results:

3.1 Primary health system costing for standard of care

Description of facility: The facility is a super speciality healthcare centre conducting multidisciplinary research related to Immunohaematology offering diagnostic services. The research and diagnosis for coagulation disorders are conducted by the department of Haemostasis and Thrombosis lab. The annual numbers of test conducted at the diagnostic lab were 3483. Among this the proportion of factor assay conducted was around 74%. For the patients undergoing factor assay around 47% were diagnosed for Hemophilia A and around 2% were Von Willebrand Disease. As per the experts there are only approx. 20 facilities in the public health setting that are doing factor assays and inhibitor screening all at tertiary level of care.

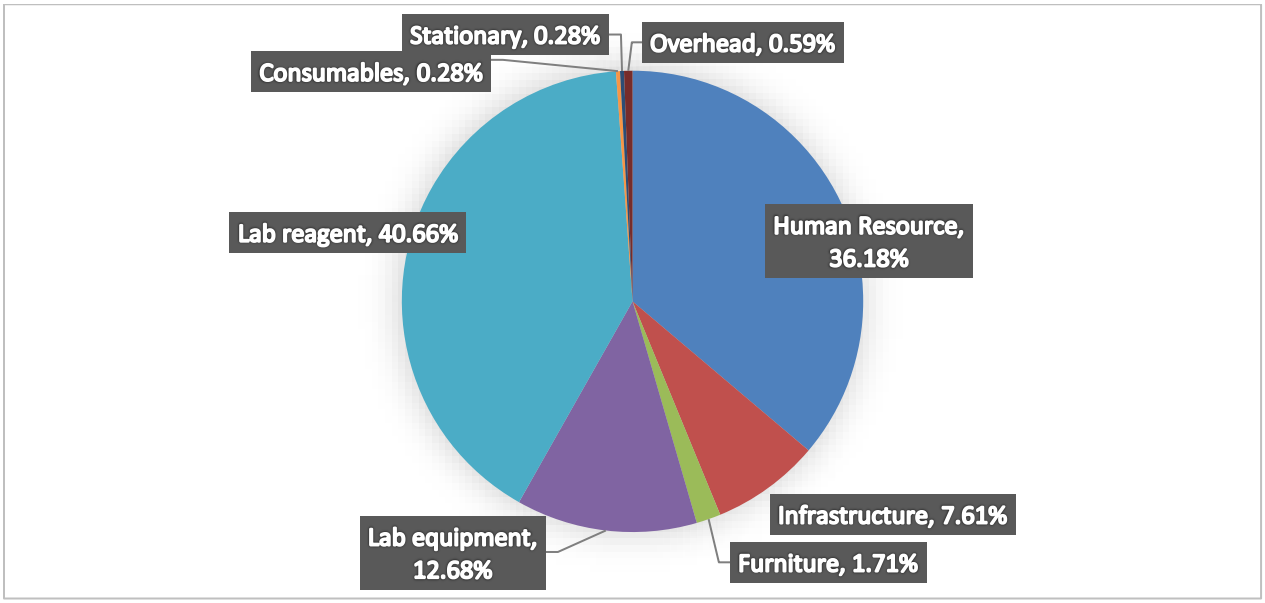
Unit Costs: The unit costs per test conducted for Hemophilia A and vWD was estimated as the ratio of the total annual costs for the testing and total number of beneficiaries in one year. It was found that the provision of diagnostic service for testing Hemophilia A/vWD at a tertiary care centre incurred a cost of INR 6646.18 per test conducted. The total annual cost of providing the diagnostic service was INR 1.71 crores.

The following table provides the proportions and cost of various components of the cost of conducting Hemophilia A and vWD test at the tertiary care facility. The major cost components were the lab reagents (40.66%), human resource (36.18%), lab equipment (12.68%) and Infrastructure (7.61%).

Table 6: Health system cost for testing Hemophilia A and vWD at tertiary care facility

Input parameters	Unit Cost (in INR)	Proportional distribution of cost	Total Cost (in INR Lakhs)
Human Resource	2404.55 (1202.27 – 3606.82)	36.18%	61.97
Infrastructure	505.96 (252.98 – 758.93)	7.61%	13.04
Furniture	113.96 (56.98 – 170.94)	1.71%	2.94
Laboratory Equipment	842.92 (421.46 – 1264.38)	12.68%	21.72
Laboratory Reagents	2702.37 (1351.18 – 4053.55)	40.66%	69.64
Consumables	18.89 (9.44 – 28.33)	0.28%	0.49
Stationary	18.42 (9.21 – 27.63)	0.28%	0.47
Overhead	39.13 (19.56 – 58.69)	0.59%	1.01
Total Unit Costs	**6646.18 (3323.09 – 9969.27)**	**100.00%**	**171.27**

Figure 3: Input-wise proportional distribution of health system cost of testing for Hemophilia and vWD at tertiary facility



3.2 Analysis of cost and outcomes of Point of Care test Kit and Standard of Care for testing Hemophilia A and Von Willebrand Disease

3.2.1 Effect of POC test Kit and SOC:

The population cohort of 0-40 years of age presenting at public health facilities with bleeding symptoms suggestive of Hemophilia A and Von Willebrand disease (vWD) in India was estimated to be 285945.

In the current standard of care multiple screening test are conducted at various levels to identify bleeding disorder. At primary facility there is no test to distinguish the type of bleeding disorder among the patients and only CBC will be preformed. . The test such as CBC will only determine the presence of bleeding disorder among the individuals. These patients are then referred to higher level facilities (secondary level) for undertaking PT/aPTT. The proportion of patient's referred to higher level is 55% (23, 24). At secondary and tertiary level for cases suspected of Hemophilia A and von Willebrand disease the most relevant tests are Prothrombin time (PT) and activated partial thromboplastin time (aPTT). The test with normal Prothrombin time (PT) and prolonged/abnormal aPTT test are suspected for Hemophilia A and vWD. Among patients with bleeding disorder the proportion of Hemophilia A is 53.57% and vWD is 7% (18, 19, 20). The utilization of healthcare services at primary is 70%, secondary is 20% and tertiary is 10% (21, 22). Based on the current level of service utilization at primary, secondary and tertiary level of healthcare, 200161 tests were conducted at primary, 167278 at secondary (including referral) and 28594 at tertiary level of healthcare. Among these patients those who are detected as normal PT and prolonged/abnormal aPTT are referred to centre of excellence (CoE) for factor assay detecting Hemophilia A and Immunoturbidimetry detecting vWD. The proportion of patients at centre of excellence is determined based on these patients detected for prolonged/abnormal aPTT and proportion of cases referred to higher facility. Total test conducted at CoE were 78150 (the coverage of current standard of care is 100%). The total number of cases detected (true positives) for Hemophilia A are 70415 and vWD are 9528 among the current cohort in the standard of care arm. The total number of cases detected combined Hemophilia A and vWD were 79943.

The Point of Care (POC) test kit provides a facility based qualitative diagnosis of hemophilia A/vWD without the requirement of referral. In the scenario 1 of the intervention arm, the total number of test conducted at primary are 200161, secondary are 57189 and tertiary are 28594. Among these the total number of cases detected using the POC test kit for Hemophilia A are 150304 and vWD are 20094. The total number of cases detected combined using POC test kit in scenario 1 for Hemophilia A and vWD were 170398.

In scenario 2 of the intervention arm, the total number of test conducted at each level of healthcare are similar to scenario 1. Among these for scenario 2, the total number of cases detected using the POC test kit for Hemophilia A are 137923 and vWD are 18439. The total number of cases detected combined using POC test kit in scenario 1 for Hemophilia A and vWD were 156363.

Compared to the current standard of care, additional the total number of cases detected in scenario 1 are 90456 (Hemophilia A 79889 and vWD 10566). In case of scenario 2, the additional the total number of cases detected are 76420 (Hemophilia A are 67509 and vWD are 8911).

Table 7: Effects for testing Hemophilia A and vWD using POC test kit and SOC test

Parameters	Intervention (POC test kit)		Comparator (SOC test)	Additional cases detected using POC compared to SOC	
	Scenario 1	Scenario 2		Scenario 1	Scenario 2
Cases detected Hemophilia A (HA)	150304	137923	70415	79889	67509
Cases detected vWD	20094	18439	9528	10566	8911

3.2.2 Cost of POC test Kit and SOC:

The health system cost for testing Hemophilia A and von Willebrand disease using the current standard of care test and POC test are estimated for the cohort of 285945 (when the coverage is 100%). The cost per case tested, cost per case detected and total health system cost are presented in the table below. The cost per test conducted for diagnosing Hemophilia A and von Willebrand disease using the POC test kit is INR 582 for scenario 1 where only POC test is administered to all at all levels and for scenario 2 it is INR 605 where POC is administered after initial screening using CBC at primary and PT/aPTT at secondary and tertiary level of care. The cost per test for current standard of care is determined to be INR 2086. The cost per test for the current standard of care is approximately 4 times higher than the test conducted using the POC test kit.

Table 8: Cost for testing Hemophilia A and vWD using POC test kit and SOC test

Parameters	Intervention (POC test kit)		Comparator (SOC test)
	Scenario 1	Scenario 2	
Cost per case test (INR)	582 (291 – 874)	605 (303 – 908)	2086 (1043 – 3129)
Cost per case detected (INR)	977 (489 – 1466)	1107 (554 – 1660)	7461 (3731 – 11192)
Total Health system Cost (in Crores INR)	16.66 (8.33 – 24.98)	17.31 (8.66 – 25.97)	59.65 (29.82 – 89.47)

3.3 Budget Impact Assessment:

The total health system cost for testing Hemophilia A and von Willebrand disease using the current SOC and POC test was estimated at varying coverage of the cohort. The total health system cost at 100%, 80% and 50% coverage is presented in table below. The total health system cost of POC test kit for both scenarios is presented and the cost saving is estimated in all cases as compared to the SOC test.

The total cost saving for scenario 1 at 100% coverage are INR 42.99 crores, at 80% are INR 34.39 crores and at 50% are INR 21.49 crores. The total cost saving for scenario 2 at 100% coverage are INR 42.33 crores, at 80% are INR 33.87 crores and at 50% are INR 21.16 crores

Table 9: Budget Impact for varied population coverage

Parameter	Intervention (POC test kit) (in crores INR)		Comparator (SOC test) (in crores INR)	Total Cost Saving (in crores INR)	
	Scenario 1	Scenario 2		Scenario 1	Scenario 2
100% Coverage	16.66	17.31	59.65	42.99	42.33
80% Coverage	13.32	13.84	47.72	34.39	33.87
50% Coverage	8.33	8.66	29.82	21.49	21.16

3.4 Sensitivity Analysis:

One way sensitivity analysis was undertaken were the cost parameters were varied by 50% above and below and the probabilities were varied by 10% on both sides. The variation of the unit cost of SOC for testing HA/VWD at tertiary level obtained through primary health system costing is presented in the Fig. 3 below.

The major effect in the unit cost of SOC for testing factor assay and immunoturbidimetry for HA/VWD obtained through primary health system costing was due to variation in input cost of laboratory reagents and human resource of approximately 20% and 18% respectively. The unit cost did not show much variation with other input costs.

Among the cost per case tested for the POC test kit, the variables that have a major impact are the price of the POC test kit. The other variables that impacted the cost per case tested for the POC test kit are health system cost, coverage at various levels, discount rate, cost of PT/aPTT, and proportion of case detected with aPTT.

Figure 4: Tornado graph of one way sensitivity of primary health system unit cost of standard of care HA/vWD test

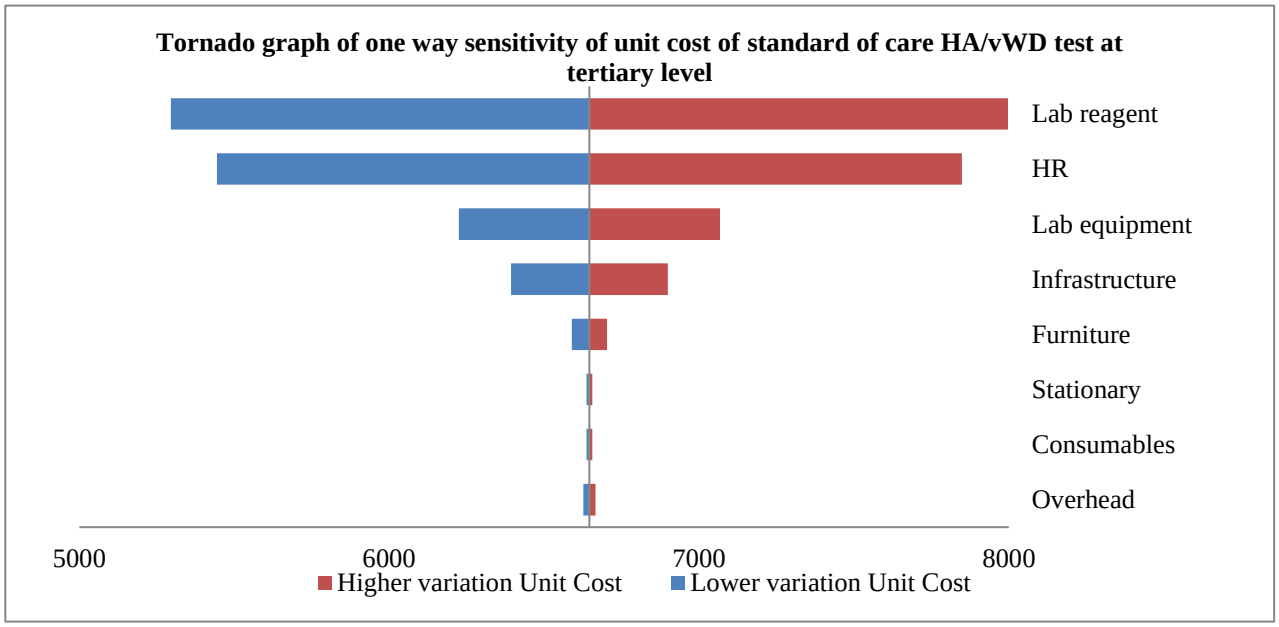
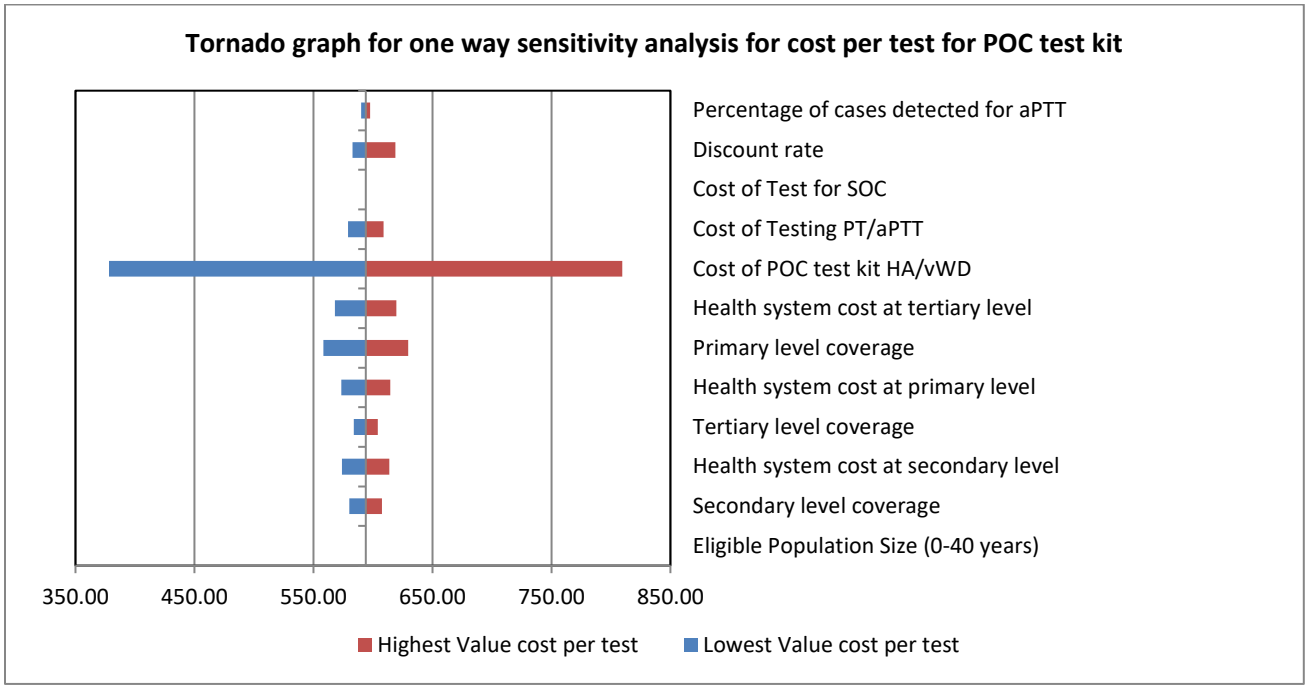


Figure 5: Tornado graph for one way sensitivity analysis of cost per test for POC test kit



Chapter 4: Conclusion, Recommendations and Implications

4.1 Conclusion

- The cost per case tested using the POC test kit for Hemophilia A/vWD for scenario 1 is INR 582 when all test are conducted using POC at all levels and for scenario 2 it is INR 605 when initial screening is done using CBC/PT/aPTT followed by POC test for suspected cases (prolonged/abnormal aPTT). While the cost per case tested for the comparator is estimated at INR 2086 which is about four times the intervention cost.

- The cost per case detected using the POC test kit was estimated INR 977 (scenario 1) and INR 1107 (scenario 2) compared to SOC test which was INR 7461. The cost per case detected is approximately 7 times higher for SOC test than the POC test.

- The total health system cost for rolling out POC kits for screening of bleeding disorders at public health facilities including primary, secondary and tertiary levels would be INR 16.66 crores (scenario 1) and INR 17.31 crores (scenario 2) while that for currently used standard of care accounts to INR 59.65 crores. The total cost saving in both the scenarios of POC test kit as compared to the SOC test is more than INR 42 crores thus reducing the health system cost approximately by 3 times.

- The additional number of cases detected due to use of POC test kits (Haemophilia and vWD) accounts to on an average 83 thousand cases which would have been missed using the current standard of care regimen.

4.2 Recommendations

- The Point of Care test Kit for Hemophilia and von Willebrand Disease can be considered suitable qualitative diagnosis of individuals with bleeding disorder or those presenting with bleeding symptoms suggestive of Hemophilia A and von Willebrand Disease.

- For quantitative analysis of the cases in terms of severity and requirement of factor through prophylaxis treatment factor assays will be need once diagnosed.

- The kits should be made available at all levels of care (primary, secondary and tertiary) in public health facilities which will substantially improve the access for patients with Hemophilia A and von Willebrand disease detected additional number of cases.

- The public health system need to be strengthen to provide management and treatment for the additional cases detected through improved access to diagnosis and early detected of patients using the POC test kit.

- The government need to formulate standard procedures for utilization of the POC test kit and referral following detection for management and treatment.

4.3 Policy Implications

- The POC kits for Hemophilia A and vWD are suitable for primary facility based screening as it requires basic lab facilities and can be used without technical expertise ensuring early diagnosis of common bleeding disorders such as Hemophilia and vWD compared to current standard of care which requires multiple diagnostic tests and expensive lab machinery along with technical expertise currently available at very few speciality healthcare facilities of the public health system.

- The POC test kits play a critical role in improving the access to diagnosis for patients of Hemophilia A and von Willebrand diseases.

- Additionally, the glaring difference in the cost per case tested, cost per case detected and health system cost compared to comparator (standard of care) makes the intervention (POC kit) distinctly eligible as a qualitative diagnostic tool for public health facility. The POC test kit provides a differential diagnosis for Hemophilia A and von Willebrand disease. This would substantially reduce the cost and time for diagnosis and ensure early treatment initiation for Hemophilia and vWD patients thus implying reduced out-of-pocket expenditure, early diagnosis, improved management and better quality of life.

- Considering the current scenario, where there is no single diagnostic tool available for identifying common bleeding disorders in primary care settings and patient referral to secondary and tertiary levels depends on the expertise of the medical practitioner in suspecting bleeding disorders, the POC kit implies rapid detection of Hemophilia and vWD patients which would have been missed or may have encountered delayed diagnosis under the currently available settings.

- The faster detection of additional cases of other bleeding disorders along with rapidly diagnosed Hemophilia A and vWD cases due to launch of POC kits will require readily available additional treatment and management facilities within the current health system to cater to the needs of patients with bleeding disorders.

- The total health system cost saving estimated for the current analysis is based on the hypothesis that the current standard of care caters to 100% coverage and availability of services. Hence, a differential cost saving at varying coverage (100%, 80% and 50%) is also provided in the budget impact. Thus in reality the health system cost will bear additional expenditure in terms of more cases tested, detected and needing treatment.

- The study findings also imply the need for OOPE study for diagnosis of common bleeding disorders considering the stark difference in the cost per case tested between the POC kit and current standard of care in currently disorganized and unsystematic setup for diagnostic care involving high partaking from the private diagnostic facilities.

4.4 Limitations of the study

- The primary health system cost for the factor assay in the standard of care was derived from a single centre of excellence facility due to limitation of time and accessibility to facilities. In India there are only very few facilities that have the infrastructure available for factor assay for bleeding disorder.
- The health system cost for screening of bleeding disorder using CBC is not estimated separately as there is no data. Also these tests does not need expertise or expensive equipment/reagent, hence the cost was considered part of the investigation cost included in the OPD cost derived from the NHSCD.
- The current analysis is only limited to cost per case tested and cost per case detected. Due to unavailability of data the economic evaluation outcome in terms of ICER was not derived.
- Cases referred from primary to higher levels in comparator arm have assumed only 75% being tested.

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