HHCN Recommendations on Policy & Protocols for selecting the right product for Optimal haemophilia care in India

- the first national guidelines from the national experts-

Haemophilia & Health Collective of North®

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Compiled by

Naresh Gupta

on behalf of

Haemophilia & Health Collective of North®

ABOUT *HHCN*
Haemophilia & Health Collective of North®

Haemophilia, a rare blood disorder in which the blood does not clot adequately, from an intrinsic genetic mutation affecting two clotting proteins- Factor VIII or Factor IX, separating the Haemophilia into two - Type A or B respectively. This deficiency can become life-threatening, and amongst the survivors frequently goes with long lasting musculoskeletal disabilities. Though present since birth or earlier, the disease may become damaging at any time, with bleeds that are spontaneous or principiated by trauma. It is the boys who show up the disease, the girls are made stronger to defend its brunt effectually. The numbers are small, with a universal incidence of the common haemophilia-A estimated at about 1 in 10,000 male births, with its severe form prevailing at 6 per 100,000 population. The latter would not thrive in their teens… without treatment.

Truly effective treatments started coming in half a century earlier. With poor availability of treatment and its unaffordability, the plight of children in India was sad and despicable in India, until the matter reached the Hon'ble High Court of Delhi. Whereupon it was mandated to some of us to establish state-run affordable haemophilia care services, starting from Delhi. This lay down the foundations for the future **Haemophilia & Health Collective of North®**.

During the intervening period, what was started in 2007-2008 in Delhi rapidly replicated in neighbouring & far-off States, with effective advocacy and capacity building initiatives. A national network was becoming robust, with regular awareness programmes, screening and diagnosing the disease for providing the right treatment. Afterall, the benefits of targeted treatment would accrue only after a specific diagnosis is made. There was an increasing interest amongst the healthcare providers, with a niche for haemophilia. A rare disease attracting such talent… it was no longer an 'orphan disease'!

The ensuing decade and a half was immensely satisfying for all stakeholders- from patient to the administrators & policy makers. It also was the period of rapid research in development of safer and more effective drug products for haemophilia treatment- the results of *Orphan Drug Act of 1983* to in stimulating these developments.

This scenario was conducive to India in learning and gainfully exploiting the rapidly growing armamentarium of haemophilia care products and modalities. But it came with uncertainties and anxieties across the stakeholders- in the patient's mind, the treaters grasp on lack of equivalently rapid research with different opinions, and this deflected onto the administrators and policy makers feeling alienated in making the right selection for optimal care under the locally prevailing *milieu* and constraints.

Also, with these improvements, the haemophilia was no longer a 'morbid' disease, but now aspiring for near normal longevity and highest quality of life. The felt need was improving the overall 'health' in the broadest sense.

Understanding to simply these two issues, would go a long a way in elevating the haemophilia care to new heights. And in fact, will become an example for managing other health problems…when haemophilia would just be an excuse or example for comprehensive improvements.

Beginning circa 2022, these were debated, discussed and brain-stormed amongst the haemophilia fraternity to explore the modalities.. With health in India remaining a State subject, there remained diversities in haemophilia care, more so when it is a rare disease. The State health administration may have its own checks and limits esp. when it comes to a comprehensive and holistic care going beyond orthodox domains.

Finally, in early 2023, all the gathered experts in haemophilia, medical and healthcare from the prestigious Government academic and medical institutions in our India, conceived to give birth to ***Haemophilia & Health Collective of North®*** - and Prof. Naresh Gupta was entrusted to lead its execution. ***Haemophilia & Health Collective of North®*** was delivered on 03rd July 2023.

Haemophilia & Health Collective of North (***HHCN***) is a registered body of senior experienced faculty staff largely from the Government medical colleges in seven States in North India. These founder members have shown their mettle for improving the lot of haemophilia and other related blood disorders, and health in general in India. With their long experience and knowledge of ground realities and administrative functioning, the members have empowered the **HHCN** to think and recommend the best decisions in the interest of patients at large while keeping the situational constraints in mind.

The Group had no doubts about this achievement, and had concurrently started work for the first national level conference, on the theme of ***Policy, Protocols & Roadmap for Optimal Haemophilia Care in India.*** Thus, bloomed the ***Haemophilia Conclave 2023*** as the first imitative of ***Haemophilia & Health Collective of North®*.**

Haemophilia & Health Collective of North® organized a highly participative and successful ***Haemophilia Conclave 2023*** organized in New Delhi on 20 July 2023, and strived to bring together the finest medical professionals and experienced caregivers, think tanks, leaders, administrators and policymakers, and other stakeholders from across the nation, playing vital role in haemophilia care. The objective being, *inter alia*, a Delphi consensus *Recommendation For Protocols and Policies for Optimal Haemophilia Care* in resource-constraint settings.

Pursuant to this ***Haemophilia Conclave 2023*** along with the real-world experience**,** *Haemophilia & Health Collective of North®* is now releasing them as formalized ***HHCN Recommendations on Policy & Protocols for selecting the right product for Optimal haemophilia care in India.***

These are the **First National Recommendation Guidelines on Haemophilia Care in India**, and it is hoped they will be of assistance in making optimal decisions based on

scientific and real-world evidence, while keeping the local ground realities in mind. These are likely to be helpful in many a resource-constrained societies.

Haemophilia & Health Collective of North® looks forward for all constructive collaborations for patient-centred improvements in healthcare in India.

HHCN

Executive Members

	Dr. Naresh Gupta Chairperson, *HHCN*	Medical Consultant, MAMC, New Delhi & Advisor for Haemophilia, Lok Nayak Hospital, Delhi. *former* Director Professor, MAMC, New Delhi
	Dr. Kuldeep K. Koul President, *HHCN*	Ex-Professor & HOD. PG Dept of Pathology/ Blood Centre Govt Medical College & associated Hospitals Jammu
	Dr. Bilal Ahmad Sheikh Vice President, *HHCN*	Professor & HOD, PG Dept of Pathology / Blood Centre Govt Medical College & associated Hospitals Srinagar, Jammu & Kashmir
	Dr. Girish Kumar Coordinator, *HHCN*	Associate Professor Department of Paediatrics Dr Radhakrishnan Govt Medical College Hamirpur, Himachal Pradesh
	Dr. Sunita Aggarwal Secretary, *HHCN*	Director Professor Maulana Azad Medical college, Delhi & Incharge Hemophilia Day Care Centre, Lok Nayak Hospital, Delhi

	Dr. Varun Kaul Joint Secretary, *HHCN*	Assoc. Professor of Paediatrics & Haematologist Guru Gobind Singh Medical College Faridkot, Punjab
	Dr. Sujata E. Mathews Treasurer, *HHCN*	Professor of Medicine Atal Bihari Vajpayee Institute of Medical Sciences, and Dr. RML Hospital, New Delhi
	Dr. Ruby Khan Exec. Member, *HHCN*	Deputy Director Blood Cell/SBTC/Lab Services/BMW /NHM, Department of Health Bhopal, Madhya Pradesh
	Dr. T.S. Reddy Exec. Member, *HHCN*	Ex-Director, Union Public Service Commission Govt. of India
	Dr. Sumant Bhardwaj Exec. Member, *HHCN*	Advocate Supreme Court of India

HHCN MEMBERS SPEAKTH…

Dr. Kuldeep Kumar Koul

Hemophilia is a lifelong bleeding disorder & due to its chronic musculoskeletal complications and life-threatening bleeding episodes makes the PWH (persons with hemophilia) permanently crippled if not promptly and adequately treated. It is a high cost, low volume disease. Although there is no epidemiological data but it is stated that with over 1.3 lakh cases, India is home to 2nd largest population of PWH. Due to high cost of treatment, it places a huge burden on the family, society and government aided hospitals and thus poses a big challenge for resource limited nations. Over the last 5 to 10 years both the Central and State/ UT Govts have kept health department on priority list and are spending huge amount on health budget in our country.

Hemophilia is one of the best examples in Medicine where basic scientific discovery has been rapidly translated into clinical practice but there are still many challenges (that are well-known) which we need to overcome. The problem is further compounded when there is no uniform policy and protocol being followed. Although WFH has provided guide lines for management of Hemophilia but these are followed either partially or not at all as it depends mainly on the budget allocation, availability of factor concentrates and other agents, number of PWH registered, diagnostic and monitoring facilities and presence of adequately trained health care professionals in the concerned treatment centre. Hence the long-term outcome of most of the PWH is unsatisfactory.

For this reason, ***Haemophilia & Health Collective of North®*** (HHCN) was constituted which comprises of senior doctors belonging to different specialties of Medicine and from various regions of North India having vast experience in Hemophilia care. ***HHCN*** executive body meet regularly and deliberate upon various important issues related to PWH of this region. In addition, developing a bleeding disorder registry and suggestions for constituting of a regional and latter national tendering committee shall also be under consideration of *HHCN*. Focus is also on selecting the right drug and optimizing Hemophilia care in India. *HHCN* has conducted Hemophilia updates/summits and thus has gathered important information in this regard by interacting with other experts at national and regional level.

The recommended guidelines by *HHCN* shall focus on ideal treatment policy, upgrading diagnostic Pathology labs and protocol to be followed for selecting safe and appropriate clotting factor concentrates and other agents for their optimal utilization and resource available to achieve the objective of *HHCN* namely, ”Treatment for all, ***One Country One Treatment***”.

Dr. Sunita Aggarwal

While WFH guidelines exist but a Comprehensive guidelines for haemophilia management in Indian context has been a much awaited need. The *HHCN Team* has now came up with one of its kind protocol with a consensus of treaters, administrators & patient group members which will support the treating physicians on one hand , and it will also provide a reference to policymakers and payers while making budgetary allocations in each State. These policy guidelines will also ensure optimal utilization of resources and will also support better quality of life related outcomes.

It is a matter of pride that the *First National Guidelines for Optimal Haemophilia Care* in India comes out from *HHCN*.

Dr. Girish Kumar

The management of Haemophilia has undergone significant evolution over time. According to the recent 2020 guidelines from the World Federation of Haemophilia, Regular Replacement therapy (prophylaxis) is now considered the standard of care for all individuals with Haemophilia worldwide. There is now a diverse range of products, each with its own set of advantages and disadvantages.

Recognizing the urgent need for a protocol to guide the selection of the appropriate product for haemophilia care, this document has been developed. Its purpose is to facilitate healthcare professionals in the critical decision-making process associated with choosing the most suitable drug products for individuals affected by haemophilia. This meticulously crafted document aims to be a masterpiece in the treatment and management of haemophiliacs, ensuring the optimal utilization of resources for the maximum benefit of patients.

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PREFACE

In India, Haemophilia remained a rather neglected 'orphan disease' until the 2007-2008 when first fully comprehensive haemophilia care centre, HDCC, was established MAMC & LNH, New Delhi under a mandate given to Prof. Naresh Gupta. This haemophilia care was ushered into the neighbouring State health services with their advocacy and capacity building, and within a decade almost all States and UTs were providing Haemophilia Care- a matter of great pride for HDCC to take it across the country.

Over the past decade and half, the developments in haemophilia care moved great strides with newer innovations, which has made the plight of haemophilia fraternity so much improved. The rapidity of this expansion in haemophilia care treatment modalities came with some uncertainties and anxieties amongst not only patients but other stakeholders including the treaters, administrators and policymakers. Regular meetings of like-minded public-oriented experts have been conducting regular scientific meetings, but has left much to eb desired. A need for more cohesive and consensus approach was palpable from all corners. This is when *Haemophilia & Health Collective of North* was born in 2023.

Haemophilia & Health Collective of North (HHCN) is a body of senior experienced faculty staff largely from the Government medical colleges in seven States in North India. These founder members have shown their mettle for improving the lot of haemophilia and other related blood disorders, and health in general in India. With their long experience and knowledge of ground realities and administrative functioning, the members have empowered the HHCN to think and recommend the best decisions in the interest of patients at large while keeping the situational constraints in mind.

Haemophilia & Health Collective of North® soon organized a highly participative and successful '***Haemophilia Conclave 2023***' on 20 July 2023 in New Delhi, striving to bring together the finest medical professionals and experienced caregivers, think tanks, leaders, administrators and policymakers, and other stakeholders from across the nation, playing vital role in haemophilia care. The objective being, *inter alia*, a Delhi consensus recommendation for protocols and policies for optimal haemophilia care resource-constraint settings.

At the ***Haemophilia Conclave 2023***, focussed sessions offering a deep dive into key issues that can potentially transform the future of haemophilia include Pharmacologic Treatment of Haemophilia, Non-Factor Therapy for Haemophilia, Are Newer Pharmacotherapy Really Worth the Money and Resources?, The Need for Uniform Treatment Policy & Protocols in India, Optimal Care in Haemophilia in

India, Role of Physiotherapy & Occupational Therapy, Social Worker, and Psychology in Haemophilia Care, and more. The deliberations were intensive and of high quality as evident from the feedback and the ensuing recommendations.

We are happy to put together all this great effort in this document and releasing the ***HHCN Recommendations on Policy & Protocols for selecting the right product for Optimal haemophilia care in India.***

This is the first effort in the country, and will surely benefit from constructive criticism. Meanwhile, it is our sanguine hope that these recommendations will be perused by the different State administrations for optimizing health equity in haemophilia care. It is an expensive treatment but comes with unsurpassable benefits by 'resurrecting the dead children back to normal life longevity and quality'

With the Very Best Wishes!

Naresh Gupta

EXECUTIVE RECOMMENDATIONS

I. Introduction and Dilemma

HAEMOPHILIAS are largely a group of *Disorders of Bleeding* caused by genetic mutations in the sex chromosome-X, resulting in functional loss from the quantitative or qualitative abnormalities in either clotting Factor VIII or clotting Factor IX, thereby segregating the two into Haemophilia-A and Haemophilia B respectively. This defect is estimated to occur in one in 5,000 live male birth for Haemophilia-A and one in 20,000 live male birth for Haemophili-B, and often runs in families. However, about a third of the cases develop amongst healthy families from *de novo* mutations. Girls are generally resistant to clinical fury of Haemophilia, and lead symptom free life.

The haemophilia manifests as bleeding, most frequently (80%) involving the large joints like knees, ankles, elbows, hip and wrist; followed by deep bleeds affecting large muscles of the body. More sinister are the bleeds affecting head/ brain, neck, chest cavity, and abdominal and pelvic cavity and deeper organs and retroperitoneum including iliopsoas muscles. Any of these bleeds carry a potential to cause an on-going, long-term damage to the affected and the adjoining areas… which is where it differs from other joint bleeds in healthy individuals. Haemophilia bleeds can expand the tissue growth as if malignant, giving rise to tumours called the pseudo-tumours (which though non-cancerous are equally damaging). The bleeds may occur after a trauma- mild or severe- or medical or surgical operation in an undiagnosed patient. More often, it occurs spontaneously even when patient is resting.

Without treatment, these boys with severe *Haemophilia* may not survive through their teens, and that too with extreme dependency, which carries a huge burden on the patient, his family, the society, the healthcare infrastructure and the Nation.

Whereas with currently available treatment, these children would grow and develop normally, with near-normal life span, getting educated and gainfully employed in best of manner. Their physical disabilities and the quality of life starts switching back to normal. And if pre-emptive treatment is given as regular replacement of the deficient protein Factor VIII or Factor IX, the life remains nearly normal without disabilities and thus tending towards a normal life span. Only a few genetic diseases can boast of such resurrection back to normal productive life!

This by itself is a very strong moral, ethical and scientific reason for treating them from childhood; and which mandates suspecting, screening and diagnosing the patients with Haemophilia before partaking the benefits of new treatments, with expanding repertoire of inventive drug products (*vide infra*).

This is true of the newer treatment products, produced using recombinant technology rather than from processing the human blood. Though all these strive towards restoring normal physiological clotting process, there is significant dissimilarity at the backend amongst these products- this adds to dilemma and uncertainties in choosing the right product for a given patient, especially in the light of still not perfect scientific

information on all of them. This still remains an enigma for the stakeholders including the policymakers, administrators and haemophilia care treaters in any country, more so in developing, resource constraint countries owing to expensive nature of treatment.

To wit, in the United States, haemophilia is among the top 10 therapeutic categories for the pharmacy spending and is the fifth most expensive speciality condition for medical-benefit spending (*UnitedHealth* Group, 2014. *UnitedHealth Center for Health Reform & Modernization*). With a similar scenario across the globe, the haemophilia fraternity is reaping huge benefits from these remarkable innovations. In India too, there is a big increase in the use of haemophilia drugs over the past 15 years, and the results of this single intervention are transforming the lives of these children who are now developing into highly qualified productive citizens as professionals, doctors, professor, , charted accountants, administrators, policy makers after graduating from prestigious institutions like the IITs, other engineering, STEM, management streams. They hold prestigious positions in the society, thereby contributing to personal empowerment, to family wellbeing, to the societal and national productivity, economy and GDP, and to the UN Sustainable Development Goals, SDG-1, SDG-2, SDG-3, SDG-4, SDG-8, SDG-10, SDG-16, and SDG-17 by invoking measures to reduce child morbidity & mortality, and their improved survival. No doubt, the policy support from Government of India such as their inclusion under the *Rights of Persons with Disabilities 2016* Act is immense and unique in the world.

The policy for using and choosing the right drug products for haemophilia care still remains a challenge, keeping in view the health equities and the interests of haemophilia fraternity. It also remains a State responsibility in resource-constraint countries.

II. Scope of this report on HHCN guideline recommendations for haemophilia Care

This report covers the guidelines for choosing from amongst the different drugs approved for specific treatment of common haemophilia disorders and are available in India.

This report does not intend to elaborate on the older 'no longer advocated products' like FFP or cryoprecipitate etc.

Nor does it cover the specific details on treatment of haemophilia patients with inhibitors, which is complex and not easily practised owing to its cost and ground realities. These are currently provided on life-saving emergency basis on as available basis.

This report also does not attempt to include the non-drug interventions or the supportive treatments such as surgical, nursing, physiotherapy, psychosocial support, rehabilitation etc.

Also, the issues of haemophilia screening and diagnostic infrastructure or pre-marriage or prenatal testing are beyond the scope of this document. Likewise, for other non-drug

interventions under the IEC, advocacy, capacity building, advocacy, empowerment etc. is also not addressed in this document.

III. Drug products for haemophilia- Developments and Safety

During the 1950s and 1960s, the mainstay of treatment of haemophilia-A was with the miniscule amount of clotting Factor VIII present in fresh frozen plasma (FFP). For Haemophilia-B, a very large volume would be required owing to even smaller fraction of clotting Factor IX in FFP. This generally necessitated hospitalisation. For want of more concentrated source of clotting Factors, this practise was continued for decades in resource-constrained settings. The innovation of 'cryoprecipitating' – made from freeze-thawing plasma – was an improvement providing incremental Factor VIII. Nevertheless, it all remained insufficient, inconvenient and fraught with side effects. Both the FFP and Cryoprecipitate, also known as "*Cryo'*, were processed in blood banks and have now been given up for treating haemophilia.

Following the 1960s, the scientists developed methods of concentrating the more purified form of clotting Factor VIII and IX, which could be technologically be achieved only by pharmaceutical industries, and which required processing plasma from millions of blood donors with due precautions for safety and quality. Processing was also necessary for removing risk of blood-transmitted infections, *inter alia*, Hepatitis- B, C, and HIV viruses. These are a risk for the blood plasma derived clotting factors.

Two prime developments in 1980s contributed majorly to development of drugs with better efficacy, safety, and adherence.

One was the HIV pandemic of the 1980s, affecting the haemophilia community from the blood plasma derived clotting Factor concentrates of varying purity and viral inactivation. Haemophilia in fact was the reason for bringing the HIV epidemic out in open. Blood products carried risks of transmitting HIV. Haemophilia community bore its brunt.

The other was the impact of the implementation of *Orphan Drug Act, 1983* in the United States, as it provided incentives for development of drugs for orphan diseases under which haemophilia qualifies universally.

Improved availability of drugs meant better treatment. Initially, the haemophiliacs would receive drug treatment in episodic manner as '*On-Demand therapy'* i.e., only after patient suffered a bleed. It was unscientific, and unlike the patients with Diabetes mellitus who are deficient in *Insulin* received insulin on regular replacement basis rather than limiting it to *Episodic*/ *On-Demand* after they had a complication of hyperglycaemia or ketosis. The scientific studies attested to the significant benefits of *Regular Replacement Therapy, RRT* (was called *Prophylaxis* previously).

Moving forward to RRT from the *Episodic/ On-Demand* did not stop all bleeds in haemophilia. The frequently injections of drug products, two or three times a week was not convenient to patients and affected adherence.

This was addressed by extending the '*Half-Life'* of drugs using innovative technologies. These proved to be a game changer, esp. for clotting Factor IX for Haemophilia-B whereas the gains in Factor VIII were more moderate. The latter clotting Factor VIII for Haemophilia-A which constitutes nearly 85% of all haemophilia awaited further improvements.

There is an intrinsic limitation to sufficiently increase the '*Half-Life'* of Factor VIII, and was overcome with the introduction of novel monoclonal antibodies that mimicked and bypassed the Factor VIII function dependent step in the clot-formation cascade. This *Non-Factor Therapy* (NFT) came with collateral benefits in form of unsurpassed half- life as high as 4-5 weeks (against less than half day for natural clotting Factor VIII), higher potency, with easy administration in the skin. It was free from the risk of transfusion transmitted infection. Further, there was no risk of inducing antibodies against clotting Factor VIII- a risk associated with all blood-derived clotting Factors with potential to inhibit efficacy of injected clotting Factor in ~30% patients.

Prior to NFT, treating the Haemophilia-A patients was difficult, with long term side effects. Treatment of haemophilia patient with *Inhibitors* is expensive. *Non-Factor Therapy* is equally effective in this sub-set of patients. All this would go to improve patient adherence, with better treatment outcomes.

In brief, the 1980s was the period innovations of creating 'human' clotting Factors VIII and IX in laboratories using the recombinant technology, with potential to churn out huge volumes of safer products.

Newer inventions over the subsequent decade led to production of *Extended- Half Life* (EHL) clotting Factors, which made them more effective and convenient for patients.

More recently, this was followed by the *Non-Factor Therapy* (NFT), using products with no resemblance to clotting factors.

Many more products are likely to come into market in coming decade.

These rapid developments gave not sufficient time to the stakeholders making decisions on choosing the best from this rapidly expanding repertoire so as to use the optimal product for haemophilia in individual patients, in different settings, in different regions of the world.

The instant document is an attempt to provide an Indian guide in making right choice of drug product for the right patient.

IV. Haemophilia Disease Types and Treatment Modalities

Choice of drug products to help clot formation in haemophilia patient are life-saving and strive to bring the patient near normal life.

This document limits to choosing from the available products for treating the highly manageable congenital, genetic disorder of haemophilia. In the light of expanding armamentarium of drug products, the haemophilia disorders considered here the common Haemophilia-A (functional deficiency of clotting Factor VIII) and Haemophilia-B (functional deficiency of clotting Factor IX).

Both the Haemophilia-A and Haemophilia-B affect the same chromosome, the X-chromosome, albeit at different locations.

The biology, mutations, and science of the two clotting Factors in human physiology are so different and their respective drug product behave so differently in clinical practice and drug development. Quite strikingly, the clinical presentation of the two diseases is highly similar.

The two diseases can be distinguished on laboratory testing to identify the specific gene or the gene product which is, clotting Factor VIII and Factor IX respectively. The drug treatment differs accordingly, in choosing the correct clotting Factor VIII or Factor IX for Haemophilia-A/ Haemophilia-B respectively.

Commonly, it is the clotting Factor that is measured for specific diagnosis. The clotting Factor assays quantifies the deficiency.

Based on the level of functional Factor deficiency, the haemophilia severity is graded as:

- Severe category when clotting Factor level is less than 1% (< 0.01 IU/ml)
- Moderate category when clotting Factor level ranges between 1 to 5% (0.01-0.05 IU/ml)
- Mild category when clotting Factor level ranges between 5 to 40% (0.05 to 0.4 IU/ml).

This grading of severity is applicable to both the Haemophilia-A and Haemophilia-B.

Since this severity tends to parallel the clinical severity, it is often considered a crude guideline to dictate the severity of treatment required to achieve the desired objectives, especially for emergency bleeds.

As stated above, the standard of care in haemophilia treatment is RRT, *Regular Replacement Therapy* (also called *Prophylaxis* in past), with the *Episodic* or *On-demand* protocol reserved for managing any emergency bleeds/ situations.

V. Drug Products for Haemophilia Care

Globally, there are several dozen drug products approved for treatment of Haemophilia-A and Haemophilia-B; a large number of them are accessible in India.

Drug Products for Haemophilia (available in India)
The following is a list of drug products currently available in India for haemophilia care, as per above categorisation.

A. Drug products for Haemophilia-A

1. *Clotting Factor Therapy* (CFT)- blood plasma derived (pd), standard half-life (SHL) drug products

   a) pd SHL Factor VIII method M, monoclonal purified (as *Hemophil M*)
   b) pd SHL Factor VIII purified freeze-dried (as *Immunate*)
   c) pd SHL Factor VIII (as *Humate-P*)
   d) pd SHL Factor VIII (as *Hemorel-A*)
   e) pd SHL Factor VIII (as *Factocell VIII*)
   f) pd SHL Factor VIII (as *Optivate VIII*)

2. *Clotting Factor Therapy* (CFT)- blood plasma derived (pd), extended half-life drug(EHL) products
   a) No *such product available in India*

3. *Clotting Factor Therapy* (CFT)- recombinant technology based (rt), standard half-life (SHL) drug products
   a) rt SHL Factor VIII *turoctocog alfa* (as *Novoeight*)
   b) rt SHL Factor VIII *octocog alfa*] (as *Avdate, Recombinate)*

4. *Clotting Factor Therapy* (CFT)- recombinant technology based (rt), extended half-life drug(EHL) products
   a) rt EHL Factor VIII *turoctocog alfa pegol* (as *Esperoct*)
   b) rt EHL Factor VIII *rurioctacog alfa pegol* (as *Adynovate*)

5. *Non-clotting Factor Therapy (*NFT)- recombinant bispecific *monoclonal antibody* (rt), extended half-life (EHL) drug products

   a) *Emicizumab,* recombinant bi-specific monoclonal antibody *(*as *Hemlibra)*

B. Drug products for Haemophilia-B

6. *Clotting Factor Therapy* (CFT)- blood plasma derived (pd), standard half-life (SHL) drug products

   a) pd SHL Factor 9 freeze-dried (as *Immunine*)
   b) pd SHL Factor 9 (as *Factocel IX*)

c) pd SHL Factor VIII(as *Replinine IX FC*)

7. *Clotting Factor Therapy* (CFT)- blood plasma derived (pd), extended half-life drug(EHL) products

a) No *such product available*

8. *Clotting Factor Therapy* (CFT)- recombinant technology based (rt), standard half-life (SHL) drug products

a) rt SHL Factor 9 (as *Rixubis*)

9. *Clotting Factor Therapy* (CFT)- recombinant technology based (rt), extended half-life drug(EHL) products

a) Rt EHL Glycopegylated Factor 9 (as *Refixia*)

10. *Non-clotting Factor Therapy* (NFT)- extended half-life drug(EHL) products

a) No such product available as yet

C. Other Drug products for Haemophilia with INHIBITORS – (known as Bypassing Agents (BPA)

21. *BPA - activated Prothrombin Complex Concentrate*, aPCC

a) Anti-inhibitor, steam-treated, Prothrombin Coagulant Complex (as *FEIBA*)

22. BPA - eptacog alfa FVIIa

a) Recombinant activated Coagulation Factor VIIa (as *Novoseven*)

D. Other Drug Products for haemophilia available in India under Humanitarian Aid Project of *World Federation of Haemophilia*

Several of the haemophilia treatment drug products (belonging to above-mentioned categories) are being made available in substantial quantities over past several years, to *Haemophilia Federation of India* by the World Federation of Haemophilia.

Some of these drug products, esp. if not in public domain, may be with approval of Government of India, routed through Ministry of Health FW.

Though all these 'donated products' should be under public domain with equal opportunity to every needy patient in India, it is not so. These are being appropriated solely by HFI in discretionary and arbitrary manner, without transparency or

equitability. There are glaring conflict of public interests, not being equally accessible or available to the haemophilia community at large.

However, since no details are available on public domain on their availability or utilisation for the common patient in India, their inclusion under the instant guidelines on Policy & protocols is not possible. Though they constitute substantive quantities.

VI. Evolution of availability of drug products for Haemophilia in India

2007
Hemophil M
Immunate
Immunine
Feiba

2008
Hemorel

2010
NovoSeven

2011
Recombinate

2014
Advate
NovoEight

2019
Hemlibra

Some pharmaceutical entities providing haemophilia care drug products in India (in alphabetical order)

- *Alpha Drugs*
- *Intas Pharmaceutical Limited*
- *Novo Nordisk India*
- Pfizer India *Limited*
- Reliance Life Sciences
- Roche India
- Takeda Biopharmaceuticals India Private Limited (formerly Baxalta Bioscience India Pvt. Ltd.)

VII. Categorising drug products for guidelines on Policy and Protocols

With myriad of drug products for haemophilia, it is important to set aside the minor variations and nuances of individual drug product when doing policies and protocols. It would make it make it easier if 'the similar' are clubbed under one category, for the purpose of public procurement and drug availability.

For this, the drug products may be described under following four variables based on pharmacologic properties:

i) **Target Type –** whether effective for treating haemophilia-A or haemophilia-B or both Haemophilia-A & haemophilia-B

ii) **Product Type** - whether the drug product is akin to the naturally occurring (missing) clotting factor or it is an innovative novel 'non-clotting factor' product such as monoclonal antibody or a product belonging to bypassing agent group.

As of date, all but one drug products available in India are natural clotting factor based (can be referred to as "*Clotting Factor Therapy*" as against the "*Non-Factor Therapy*" for novel products).

iii) **Product Source** - whether the drug product is extracted from human blood/ plasma or whether it is synthesised in laboratory-based on recombinant technology.

iv) **Product Half Life** - This refers to the property of how long does the drug product remains effective in the patient body after its administration.

The process of categorisation is described below:

Assigning an abbreviated label upfront to the given drug product based on the above variables:

i) Whether this drug product is for use in Haemophilia-A or Haemophilia-B or both …

(suffix with *-A* or *-B* or -A&B)

ii) Which category does this drug product belongs to- *Clotting Factor Therapy* (CFT) or *Non-Factor Therapy* (NFT) or *By-Passing Agent* (BPA)

(assign *CFT or NFT or BPA*)

iii) If CFT category, which sub-category does this drug product belongs to- *Plasma Derived (pd)* or to *Recombinant Technology*
(assign pd or rt)

iv) Which sub-category does this drug product belongs to- *Standard Half Life* (SHL) or *Extended half Life (EHL)*
(assign *SHL or EHL*)

The above four are variables of prime significance in categorising a given drug products for haemophilia care.

Any drug product will necessarily have qualifying variables under each.

Next step: Assigning a CATEGORY number to the given drug product, based on the four variables, in abbreviated format .

Thus, the categories will go as under:
CAT1 :xxxx
CAT2 :yyyy
CAT3 :zzzz
and so on…

where the suffix xxxx, yyyy, and zzzz define the above four variables (drug properties) of the drug product.

In essence, these categories will read as under:
CAT1 :pdSHL-B
CAT8 :rtSHL-B
CAT9: rtEHL-B
CAT5:rtNFT-A…
And so on…

Table 1 provides a comparative details of all currently available drug products for haemophilia care, under the 12 Categories, from CAT1 to CAT22. It shows their relevant properties and utilisation for haemophilia care in cross-checked and relational view.

Please note this document does not purport to detail the pharmacology of individual drug product relating to pharmacokinetics, pharmacodynamics, side-effects, drug interactions, warnings and precautions etc. These remain solely under the domain of the treating physician.

The information that follows on usage of the ‘drug product categories’ is indicative and solely for the guidance of stakeholders for making it easier to comprehend a given drug product for policy, protocols and the procurement.

TABLE-1 Assigning Category to any drug/product for treating Haemophilia, based on its utility

CATEGORY	Properties of drug product	No of drugs commonly available in India	Useful for Haemophilia -A	Useful for Haemophilia -A with Inhibitors	Useful for Haemophilia -B	Useful for Haemophilia -B with Inhibitors	Production is Blood/ plasma derived	Production is recombinant Lab based
CAT1:	pd SHL-A	6-8	Yes	No	No	No	Yes	No
CAT2:	pd EHL-A	NONE						
CAT3:	rt SHL-A	2-3	Yes	No	No	No	No	Yes
CAT4:	rt EHL-A	2	Yes	No	No	No	No	Yes
CAT5:	rt NFT-A	1	Yes	Yes	No	No	No	Yes
CAT6:	pd SHL-B	3-5	No	No	Yes	No	Yes	No
CAT7:	pd EHL-B	NONE						
CAT8:	rt SHL-B	1-2	No	No	Yes	No	No	Yes
CAT9:	rt EHL-B	1	No	No	Yes	No	No	Yes
CAT10:	rt NFT-B	NONE						
CAT21:	pd BPA aPCC -A&B	1	Yes	Yes	Yes	Yes	Yes	No
CAT22:	*rt* BPA FVIIa- A&B	1	Yes	Yes	Yes	Yes	No	Yes

NOTE:

i) This Category Number *alone* would become the key to refer to any drug product anytime.

ii) The descriptive abbreviated variables are ingrained in the Category Number and hence need not be of concern to any longer.

iii) The CFT for Clotting Factor Therapy, is omitted because its sub-categories *SHL* or *EHL* speak for it

iv) CAT11: to CAT20: have been intentionally left blank. More CAT: numbers can be added to this format in appropriate slots as and when newer drug products become available

Thus, any drug product for haemophilia treatment can be assigned any of the twelve CAT: number as per Table 1. And thereafter, refer to it simply by its assigned CAT: number.

This categorisation will be adhered to in the present document in the *HHCN guidelines* for haemophilia treatment protocols.

It is hoped that this will simplify the understanding of various drug products and thereby in the decision making by the policymakers, administrators and other stakeholders in making the right choice for better haemophilia care.

VIII. Basics on using the Drug Products In Haemophilia Treatment

First, the Clotting Factor Therapy (CFT) drug products:

Half-Life of Drug Products
The standard and scientific drug treatment of Haemophilia is with *Regular Replacement* of the deficient protein namely, clotting Factor-VIII / Factor-IX in the body, and is best referred to as the *Regular Replacement Therapy* (RRT). It is similar to regular replacement of the deficient insulin or insulin-like product in patients with *Diabetes mellitus*.

The missing proteins need to be replaced frequently, depending on their half-life. The frequency is often every 1 to 3 half-life.

A drug product's half-life is a function of its metabolism in the body and is denoted by the number of hours it takes for its level come down to half in the body.

The half-life of naturally occurring clotting Factor-VIII in human body averages 8-12 hours and is replaced from twice to once in a day. For Factor-IX, it is 18-24 hours, and requires repeat dosing once every one to two days.

The drug products mimicking this natural product half-life of clotting Factor are the *Standard Half-Life* (SHL) products.

By modifying the *SHL* factors, the half-life can be extended to 18-20 hours and to 100 hours for Factor-VIII and Factor-IX respectively, and are designated as *Extended Half-Life* (EHL) Factors.

Protocols for Treatment
The protocol of regimens for haemophilia treatment are RRT, *Regular Replacement Therapy* (also called *Prophylaxis* in past), and the *Episodic* or *On-demand* protocol reserved for managing emergency bleeds/ situations.

This RRT may use a Standard Protocol, with posology based on results of scientific research - which defines the drug dose and the interval or frequency of administration of clotting Factor.

There are variations to this **Standardised Protocol** of treatment, and are practised to individualise the treatment to individual needs.

These variants are often based on the premise that every individual reacts somewhat differently to a given drug product, and that every patient has different needs based on his lifestyle.

- **PK-driven protocol:** when the drug posology is individualised based on his pharmacokinetic variations in handling the drug by his body. This provides better efficacy from improved trough levels and may save on overall drug consumption and hence the costs.

- **Phenotype-driven protocol:** when the drug usage is individualised based on his clinical bleeding behaviour and which parallels the bleeding pattern and activity

- **Convenience-driven protocol:** when the drug usage is individualised to improve compliance and adherence based on strategies for RRT regimens in pivotal clinical trial programmes

Drug Posology
Body of every haemophilia patient reacts and handles the drug differently. There is no single dose for any drug product for haemophilia care and requires calculation. The purpose of treatment is to raise the functional blood level of deficient clotting Factor to a *desired level* as dictated by the clinical context

The degree of clotting factor deficiency in haemophilia may range from 0% upto 45% of a normal individual; and is graded as Severe /Moderate /Mild for blood levels <1% /1 to <5% /5% to 45% respectively. The clinical bleeding in haemophilia tends to parallel the severity of this deficiency. Hence the pre-treatment or baseline level of clotting factor is taken into consideration when calculating the dose.

The drug product metabolism varies from one person to another, a simplified practice is to calculate the Dose on per Kg body weight, which is a prime determinant.

This works generally well, but may need adjustment for the age, body weight, obesity level, blood groups, lifestyle, activity level, and work profile and other constitutional metabolic differences.

These get accounted for in the PK-Driven protocols, which thus become more scientific and rational though somewhat cumbersome to practice. These PK-based regimens may save on the overall drug consumption.

Another variation in protocols relate to reducing the drug dose to less than standard, and are known as the **Intermediate** and **low-dose RRT** protocols. Though gaining popularity because of lost cost, these await further research and real-world experience before getting them adopted as standard. Nevertheless, these save on consumption of drug products and add to health equity. The final word on their scientific validity awaits results from larger studies.

Now, the Non-clotting Factor Therapy (NFT) drug products:
There are only limited number of NFTs available at present, though several more are in pipeline. At present, the sole drug product available in India is *Emicizumab*.

Non-Factor Therapy (NFT) drug products are shown equally effective, with additional advantages such as its efficacy in patients with Factor VIII Inhibitors, longer duration of efficacy, and easy administration via 'subcutaneous' route on monthly basis.

The *Bypassing Agents* (BPA) are drug products that often play the role of rescue drugs to treat emergency bleeds in difficult scenarios such as haemophilias with Inhibitors .

Inhibitors in Haemophilia
Any injected foreign protein runs risk of inducing development of 'defending Inhibitor antibodies' against the injected product.

The haemophilia treatments with '*Clotting Factor Therapy'* (CFT) may generate a defensive rejection response within the body which considers the injected Factor as a foreign invading protein. This response is in the form of new 'antibodies' to defend the body against what is construed as foreign protein. When these antibodies start neutralising the injected protein Factor, they are termed as *Inhibitors*.

All clotting factor-based therapies run the risk of developing these *Inhibitors* to the injected clotting Factors. Such scenario occurs in nearly 30% of Haemophilia-A and much fewer 3-5% of treated haemophilia-B patients.

If significant, here are ways of managing these '*Inhibitors'*- simplest being desensitisation of the patient using the same product (Immune Tolerance Induction or ITI)

Hence drug products are required that bypass the CFT drug products. There are three such drug products available as '*By-Passing Agents'* (BPA), namely

i) activated recombinant Factor VII (as *Novoseven*),
ii) activated prothrombin complex concentrate, PCC (as *FEIBA*), and
iii) non-factor product Emicizumab (as *Hemlibra*). This product cannot used in emergency bleeding situations.

IX. Description of the Categories of Drug Products for Haemophilia Treatment

DRUG PRODUCTS FOR HAEMOPHIA -A

There are 4 such category drug products
CAT1: pd SHL-A
CAT2: pd EHL-A
CAT3: rt SHL-A
CAT4: rt EHL-A
CAT5: rt NFT-A

CAT1: pd SHL-A
Plasma-derived concentrates are derived from the human blood donated by healthy volunteers and after screening it for safety. These products have been in use for haemophilia since the 1970s.

During eighties and nineties, **CAT1:**pdSHL-A went into dispute for its risk of transmitting HIV and viral hepatitis. More stringent screening of donors and viral inactivation in CAT1: production line was resorted to with increasing success.

Nevertheless, the risk for potential transfusion of infections (and possible reactions from proteins) - known and unknown- remained. Also, the blood plasma donors possibly could not meet the increasing demand for clotting factors.

There are limited circumstances where CAT1: have some justification:

i) Based on a study linking lower rate of 'Inhibitors' with some CAT1: compared to one 2nd-generation recombinant products, some favoured its use esp. for first fifty exposures. Though it is not accepted as consensus, some user may like to adhere to this practice.

ii) The CAT1: are of different grades of 'purity.' This property gets exploited for clinical advantage for treating *von Willebrand Disease* (vWD). The clotting Factor VIII circulates in blood, bound to another clotting factor, *von Willebrand Factor* (vWF), and deficiency of which leads to vWD. Thus, an earlier CAT1: with residual vWF in the final product, may be beneficial for treating patients with *von Willebrand Disease* (vWD) in resource-constraint settings when pure *vWF* is not available or is very expensive.

Procurement for such use may be clearly documented by the user.

Other than these two scenarios, the routine procurement of CAT1: gets into procurement for its competitive cost against recombinant products.

CAT2: pd EHL-A
No CAT2: pd EHL Factor-VIII products for haemophilia-A available in India

CAT3: rt SHL-A
Recombinant technology has lot of plasticity and scope for tweaking for better products, and the CAT3: rtSHL-A products have gone through generations of incremental improvements in purifications, and safety- with the 3rd generation products being free of any extraneous proteins from any source. This makes them more palatable for clinical use.

Clinically, all of these products have met the expectations of safety and efficacy.

Treatment based on personalised PK-driven protocols may result in optimisation of dose, along with better clinical outcome. Cost-optimisation is likely to go with this practice.

Use of CAT3: also demands frequent injections similar to the CAT1: and more than the CAT4:. It is the comparative cost between the CAT1: and CAT2: that contributes to tilting the balance.

This new technology can rapidly meet the increasing demands, rather easily. This will also bring down the cost, as happened the case of insulin… after switching from animal-source to recombinant technology.

It is thus in interest of every stakeholder to move towards to recombinant technology products CAT3: and CAT4: in terms of safety and price advantage. Efficacy remains unaltered.

CAT4: rt EHL-A
The currently available **CAT4:** rt EHL-A drug products extend the half-life of clotting factor-VIII to approximately 1.4–1.6 times the corresponding CAT1: SHL. There is still some biological limit to extending half-life of Factor VIII beyond this, though recently, a new variant of has increased half-life of clotting factor VIII to 43 hours.

The CAT4: drug products add to better bleed control and better Quality of Life, from the higher trough levels and the fewer number of cumulative injections (lower by 50%). The CAT4: drug products lead to better compliance and adherence by patient, which also translates into better outcome.

The CAT4: drug products give better adherence and greater efficacy in terms of better bleed control and better Quality of Life, from the higher trough levels and the fewer number of cumulative injections (lower by 50%), and possible incremental benefits over extended use. Fewer drug doses for good haemostasis during surgery.

Treatment can be personalised with a PK-driven protocol, resulting in optimisation of drug usage and the clinical outcome. Cost optimisation is also likely.

Clinical research supports "switch to EHL (rFVIII-Fc) was associated with an improved clinical outcome, reflected by ABR reduction, and less frequent infusions, without significantly higher factor usage" (www.nature.com/scientificreports/ https://doi.org/10.1038/s41598-021-92245-5). The annual quantity used are comparable.

The provider institutions and haemophilia treaters following institutional therapy (rather than Home therapy) would save on time, space and infrastructure costs compared to CAT1:/ CAT3: drug products.
In principle, all patients with Haemophilia would benefit from rtEHL-A clotting Factors.

The only consideration may be costs, which are coming down day-by-day and competing well with CAT1:/ CAT3: drug products (*vide infra*).

CAT5: rt NFT-A
This **CAT5**:NFT-A is very different from the above categories CAT1 to CAT4, in as much as this is a novel 'Non-Factor Therapy' mimicking the function of the deficient natural clotting Factor VIII. In fact, the CAT5: drug products bypass this step in the clot formation, making Factor VIII redundant.

Since these are not true clotting Factor proteins, they are free of the fearsome side effect of the development of '*inhibitors'* to clotting factors as per present clinical data. It is highly valuable as this side effect from using CAT1: to CAT4: drug products is reportedly not uncommon, afflicting 30% of Haemophilia-A patients, with has huge cost implications in their management.

The CAT5: rt NFT-A drug products are comparatively much more potent than natural clotting factors.

The CAT5: drug products are clinically no less effective than CAT1: to CAT4: products, but have additional property of being much more longer lasting (half-life 4-5 weeks), and maintain stable effective potency over long duration, making them suitable for administration only once in a month (as against 2-3 times a week for CAT1: to CAT4: products).

The CAT5: drug products with their long-duration steady levels are preferred choice for RRT, not requiring much monitoring or dose titration.

Another big advantage with CAT5:NFT-A products is convenient mode of administration under the skin, subcutaneously without contact with blood. This is akin

to injecting insulin in Diabetes mellitus, which any patient can do anywhere with little practice.

The real-world experience is rapidly expanding its use and acceptance- in new and switchovers patients- across the globe, including India. Patient acceptance has contributed in no small way in acceptance of CAT5: drug products.

However, there are concerns with using CAT5: drug products.

i) These long-acting CAT5: drug products are not recommended for managing emergency bleeds.
ii) The CAT5: drug product may run the risk of thrombotic complications from overt coagulation. This was linked to the concomitant use of some CAT22: BPA product. After limiting this use judiciously, this complication has largely been addressed, an example of learning to tame the potent human innovations.

This drug-drug interaction now forms part of guidelines for using CAT5: drug products.

The cost remains a consideration, and is discussed below (*vide infra*).

DRUG PRODUCTS FOR HAEMOPHIA -B

There are 4 such category drug products
CAT6: pd SHL-B
CAT7: pd EHL-B
CAT8: rt SHL-B
CAT9: rt EHL-B

CAT6: pd SHL-B
Unlike Haemophilia-A, the number of drug products available for treating Haemophilia-B are fewer, reflecting on its relatively less prevalence (Haemophilia-A : Haemophilia-B : : 85:15).

Just a couple of drug products are meeting the demand across our country.

The general comments made above under CAT 1: pdSHL-A products on the efficacy and safety apply equally to this CAT6 of pdSHL-B products, with one major difference. Which is its significantly lower risk of development of 'Inhibitors', the antibodies that inhibit the clotting factor IX- in the instant case. This inhibitor risk is lower at about 3% (compared to 30% for haemophilia-A).

Incidentally, this risk for development of Inhibitor is similar with all the categories of clotting Factor IX, namely CAT6:, CAT8:, and CAT9:

The limited availability of blood plasma, and the incremental global demands and the potential concern on their safety would encourage moving towards recombinant drug products, away from CAT6:.

Nevertheless, in the hierarchy of Health Equity, this time-tested CAT6: drug product may still provide rescue in resource-constraint settings.

The CAT6: drug products suffer from the deficiency of administering frequent injections (intravenously), compared to the much more long-acting CAT9: drug products.

Cost considerations are discussed below.

CAT7: pd EHL-B
There are no pd EHL Factor-8 products for Haemophilia-B

CAT8: rt SHL-B
Recombinant technology has lot of plasticity and manoeuvrability for tweaking for improvements. The **CAT8:** rt SHL-B drug products have benefited from these newer developments, making them safer and free from extraneous elements.

Clinically, all these new products have met the expectations of safety and efficacy.

Treatment can be personalised with a PK-driven protocol, resulting in optimisation of dose and the clinical outcome. Cost-optimisation likely with this.

The use of CAT8: drug products demands frequent injections similar to the CAT6: drug products.

Often, it is the comparative cost between the two categories, CAT6: and CAT8: that disturbs the balance while selecting.

This new technology can rapidly meet the increasing demands rather easily,

CAT9: rt EHL-B
Unlike clotting Factor VIII, the current protein technology can extend the half-life of clotting Factor IX to almost x5 times.

This is indeed very remarkable achievement as it brings enormous benefits of the CAT9: rt EHL-B drug products to haemophilia-B patients, by reducing the frequency of their intravenous injections down to once in a week or 10 days. This is big change from every second-third day from CAT6:/ CAT8: products, translating into nearly 70% reduction

in frequency of injections, with better patient compliance and adherence and the Quality of Life, incremental over extended use.

And fewer drug doses to be injected for good haemostasis during surgery.

Treatment can be personalised with a PK-driven protocol, resulting in optimisation of drug usage and the clinical outcome. Cost optimisation is also likely.

All these make the CAT9: rt EHL-B the choice drug product for treatment for haemophilia-B.

Further, the provider institutions and haemophilia treaters can save on time, space and infrastructure costs compared to CAT6: and CAT8: drug products.

The CAT9: drug products are really game-changers for haemophilia-B as compared to similar products developed for haemophilia-A (CAT4:rtEHL-A) and hence deserve serious consideration for all haemophilia-B patients.

The perceptions and realities on their cost considerations are addressed below (*vide supra*). The costs also are likely to come down with time

DRUG PRODUCTS FOR BOTH HAEMOPHILIA -A & B

Currently these are limited to the bypassing agents (BPA), for their property of bypassing the function of 'clotting factors made ineffective' by the 'inhibitors.'
More products are in the pipeline.

CAT21: pd BPA aPCC- A&B
Prothrombin Complex Concentrate (PCC) is derived from the blood-plasma cryoprecipitate supernatant by ion-exchange chromatography, after removal of antithrombin and clotting Factor XI. PCC dosing products are expressed as units of clotting Factor IX.

PCC exists in two varieties:
a) 3-factor PCC
b) 4-factor PCC

The 3-factor-PCC contains factors II, IX, X, and little or no factor VII.

The 4-factor PCC contains inactive factors II, VII, IX, and X, and small amounts of heparin and protein C and S

Activated PCC (aPCC) contains inactive factors II, IX, and X similar to 4-factor PCC, however in contrast to 4-factor PCC, it contains activated Factor VII.

The sole CAT21: aPCC drug product available commercially is *FEIBA* and is relevant to use in haemophilia.

FEIBA, the sole product under CAT 21: is indicated for the treatment of bleeding episodes in haemophilia-A and haemophilia-B, with 'inhibitors' that neutralise the clotting Factors and make them ineffective. Its use is largely confined to largely emergency use in such patients for control of bleeding episodes and perioperative management.

Thromboembolic events have been reported during post-marketing surveillance following infusion of CAT21: drug product *FEIBA*, particularly following the administration of high doses (above 200 units per kg per day) and/or in patients with thrombotic risk factors or concomitantly with other procoagulants.

Monitor patients receiving FEIBA for signs and symptoms of thromboembolic events.

Use of *FEIBA* as RRT in 'haemophilia with inhibitors' is very expensive and tedious and is not practised in India and is difficult .

CAT21: drug product is not indicated for treatment of bleeding episodes from coagulation factor deficiencies *in the absence of inhibitors* to clotting Factor VIII or Factor IX in haemophilia-A and haemophilia-B, respectively.

However, CAT21: drug products may have important applications in other non-haemophilia bleeds including, *inter alia*, from the congenital or acquired vitamin-K deficiency or warfarin-induced anticoagulation.

Thus, the procurement of CAT21: may be for different diseases. Its use in haemophilia is limited to emergency bleeds in patients with inhibitors

CAT22: rt BPA FVIIa- A&B
There is only one product under this CAT22:, namely *eptacog alfa* which is a recombinant activated form of clotting Factor VII (FVIIa).

NovoSeven RT is the first and the only marketed brand available as intravenous injection.

Like other BPAs, this CAT22: drug product is largely used in Haemophilia-A and Haemophilia-B patients with 'inhibitors' for treatment of the emergency bleeds and for perioperative haemostasis control during surgery or procedure in adults and children.

It is approved for use in treatment of 'non-haemophilia' disease conditions such as congenital Factor VII (FVII) deficiency, Glanzmann's thrombasthenia or postpartum haemorrhage. These conditions are not under preview of this document.

With a very short half-life of about 2.4 hours, CAT22: drug product *Novoseven* would necessitate frequent injections.

Like other BPA CAT21:, the drug product under CAT22: is not practised for RRT in 'haemophilia with inhibitors' in India and is difficult even globally.

Also, the CAT22: drug product is not to be used for treating haemophilia patients *without* inhibitors. Hence, not detailed in this document.

X. Cost and other considerations in choosing drug products after the above Categorisation

The Standard of Care for any haemophilia patient is *Regular Replacement Therapy* (RRT) because a deficient state can result in spontaneous bleeding anytime anywhere, with consequential on-going morbidities and mortality.

The *Episodic* or '*On-Demand'* therapy may still be in practice while transiting to RRT. Nevertheless, it cannot be recommended lest it adds to avoidable morbidities in the society, and there is a dire need to move up and beyond, just like we did from the earlier blood bank components like FFP, cryoprecipitate etc

The important consideration in resource-constraint settings is the cost factor, as it is presumed the RRT may be more expensive than the *Episodic* or '*On-Demand'* therapy. While it may seem to be true if one looks at the direct cost of the drug product, it overlooks the wider tangible and intangible benefits that go to improve the patient outcome. Here cost-benefit ratio needs to include the direct and indirect costs incurred during a time interval, say on monthly basis.

While transiting to RRT from the '*Episodic'* or '*On-Demand'* (which is one-time treatment for emergency bleeds only), a middle alternative to consider may be to use '*low dose'* or '*intermediate dose' RRT* to save on the consumption and cost of drug products. It may be difficult call for some haemophilia treaters, for good reasons-afterall, these still are not standards of care.

A one IU (international unit) per kg body weight dose of clotting Factor VIII is likely to raise the blood Factor VIII by 2 IU% in patient with haemophilia-A. Based on its half-life, the dose generally needs repetition twice in a day.

Whereas in haemophilia-B, a similar dose of clotting FactorIX is likely to raise the clotting FactorIX level by 1 IU% only. However, owing to longer half-life of 18-24 hours, the dose requires repetition only once in a day only.

The clotting Factor consumption for treating Haemophilia-A or Haemophilia-B are comparable.

Cost consideration issues:

a) Direct costs
b) Indirect costs
c) Non-monetary costs

The variables are complex when it comes more recent drug products like the EHLs and NFT drug product CATEGORIES (*vide infra*).

HAEMOPHILIA-A

Only the following CAT: drug products are available for treatment of Haemophilia-A, namely

1. CAT1: pdSHL- A
2. CAT3: rtSHL- A
3. CAT4: rtEHL- A
4. CAT5: NFT - A

CAT1:pdSHL- A drug products for Haemophilia- A

All the CAT1: drug products can be used for both the *Regular Replacement Therapy (RRT)* and the *Episodic* or '*On-Demand'* therapy for emergency bleeds in haemophilia-A patients.

For reasons stated above, there is trend of moving forward from CAT1: drug products to the superior ones like CAT3 to CAT5 products.

Nevertheless, the practical considerations (cost and inhibitor risk) and the circumstances (collateral benefit for vWD patients) may justify specific procurement of CAT1: drug products (*vide supra*).

Several different brand products are available under CAT1: in the Indian market. These CAT1: blood plasma products have remained the mainstay for the treatment of haemophilia-A for the longest period of the past half a century. Initially, these were used as *Episodic* or '*On-Demand'* protocol, before moving forward to the more effective RRT protocol, which currently is the Standard of Care.

The dosing and frequency of administration for RRT is similar for all products in CAT1, and so is the costing.

However, the dosing has evolved over the decades, moving from the really 'high dose' to rather 'low-dose' regimens.

Other variables may find a particular RRT regimen more suitable for a given patient depending on his annual bleed rate (ABR), bleeding phenotype, activity level, specific needs and convenience. Such regimen may be personalised, with the pharmacokinetics

(PK-) based regimen remaining at the centre for its scientifically precise dosing albeit somewhat tedious to follow. Other variants have been invented (*vide supra)*.

CAT1: costing
Indicative drug product posology range as under:
High- Dose regimen
25–45 IU per kg body weight, thrice a week

Standard- Dose regimen
25 IU per kg body weight, thrice a week

Intermediate- Dose regimen
15-25 IU per kg body weight, thrice a week

Low- Dose regimen
10 IU per kg body weight, once or twice a week

The higher dose regimen results in better control of haemophilia, but at an economic cost.

Thus, for Standard RRT protocol of thrice weekly dosing, a Haemophilia-A patient weighing 10 Kg may require CAT1: dose of

25 IU x 10 x 3 x 4 = 3,000 IU per 4 weeks, or
3,000 x13/12= 3,250 IU per month

At an indicative cost of Rs.6 per IU of CAT1:pdSHL drug products, it translates into:
Rs.18,000 per 4 weeks or
Rs.19,500 per month

For other body weights, the above will apply in arithmetic proportion

Guidelines on parameters for selecting the drug products for prioritisation of haemophilia treatment are described in *Table 2a*, *2b*, and *Table 3*.

CAT3:rtSHL- A drug products for Haemophilia- A
All the CAT3: drug products can be used for *Regular Replacement Therapy* or the *Episodic* or '*On-Demand'* therapy for emergency bleeds in haemophilia-A patients.

Only a limited number of brand drug products are under CAT3: available in Indian market.

Recombinant technology based CAT3.:rtSHL-A drug products have gone through sequential generations of incremental improvements, purifications, and better safety-

with the 3rd generation products being totally free of any extraneous proteins of any source during manufacturing.

Though potentially safer, the CAT3.: drug products show similar efficacy as the CAT1:products.

Likewise, the treatment can be similarly personalised with a PK-driven regimen, resulting in optimisation of dose and the clinical outcome, and better cost-optimisation. The variant protocols are considered as for the CAT1: products.

The other variable that contributes to the decision of choosing between CAT3.: and CAT1: drug products is the comparative cost.

CAT3: costing
Thus, for Standard manufacturer prescribed RRT protocol of thrice weekly dosing, a Haemophilia-A patient weighing 10 Kg may require CAT3: dose of

40 IU x 10 x 3 x 4 = 4,800 IU per 4 weeks, or
4,800 x13/12= 5,200 IU per month

At indicative cost of Rs.8 per IU of CAT3:rtSHL- A drug product, it translates into:
Rs.38,400 per 4 weeks, or
Rs.41,600 per month

A high or low-dose RRT regimen will parallel the same costing ratio.

For another manufacturer prescribed RRT protocol using dosing of 25 IU per Kg thrice weekly (similar to CAT1:), a Haemophilia-A patient weighing 10 Kg may require a CAT3: dose of

25 IU x 10 x 3 x 4 = 3,000 IU per 4 weeks, or
3,000 x13/12= 3,250 IU per month

At indicative cost of Rs.8 per IU of this CAT3: drug products, the cost works out to:
Rs. 24,000 per 4 weeks, or
Rs.26,000 per month

For other body weights, the above will apply in arithmetic proportion.

Guidelines on parameters for selecting the drug products for prioritisation of haemophilia treatment are described in *Table 2a*, *2b*, and *Table 3*.

CAT4:rtEHL- A drug products for Haemophilia- A
All the CAT4: drug products can be used for *Regular Replacement Therapy* or the *Episodic* or '*On-Demand'* therapy for emergency bleeds in haemophilia-A patients.

Only two brand drug products are under CAT4: available in Indian market.

There are biological advantages of extending half-life of clotting Factor VIII, with the current CAT4: drug products extending it to approximately 1.4–1.6 times the corresponding SHL product.

This leads to better adherence by patient from fewer number of cumulative injections (lower by 50%) and better efficacy because of improved bleed control from higher drug trough levels, all translating into better Quality of Life.

Treatment can be personalised with a PK-driven protocol, resulting in optimisation of drug usage including surgeries and the clinical outcome. and the cost optimisation.

Switching over from CAT1; or CAT3: drug products to CAT4:rtEHL- A: "Clinical research supports "*switch to EHL (rFVIII-Fc) was associated with an improved clinical outcome, reflected by ABR reduction, and less frequent infusions, without significantly higher factor usage*"
(www.nature.com/scientificreports/ https://doi.org/10.1038/s41598-021-92245-5

Further, this brings down the indirect shadow infrastructural costs which tend to be much higher in the current 'institution-based' set ups in India.

CAT4: costing
Thus, for Standard manufacturer prescribed RRT protocol of dosing 50 IU per Kg every 4 days or 75 IU per Kg weekly, a Haemophilia-A patient weighing 10 Kg may require CAT4: dose of

a) For the RRT Regimen 50 IU per Kg every 4 days

50 IU x 10 x 7/4 x 4 = 3,500 IU per 4 weeks, or
50 IU x 10 x 30/4 = 3,750 IU per month

At indicative cost of Rs.14 per IU of CAT4:rtEHL- A drug product, it translates into:
Rs. 49,000 per 4 weeks, or
Rs.52,500 per month

b) For the RRT Regimen 75 IU per Kg weekly

75 IU x 10 x 4 = 3,000 IU per 4 weeks, or
75 IU x 10 x 30/7 = 3,215 IU per month

At indicative cost of Rs.14 per IU of CAT4:rtEHL- A drug products, it translates into:
Rs. 42,000 per 4 weeks, or
Rs.45,000 per month

Thus, a mandated Standard manufacturer prescribed protocol for RRT with CAT4: drug products ranges between Rs.42,000 and Rs.49,000 per 4 weeks.

Using these in 'off-label' lower-dose or higher interval RRT regimen will proportionately bring down the costing.

For other body weights, the above will apply in arithmetic proportion.

Guidelines on parameters for selecting the drug products for prioritisation of haemophilia treatment are described in *Table 2a*, *2b*, and *Table 3*.

CAT5:NFT- A drug products for Haemophilia- A

Unlike the *Clotting Factor Therapy* (CFT), CAT5: products belong to *Non-clotting Factor Therapy* (NFT).

The CAT5:NFT-A drug products can be used for *only Regular Replacement Therapy* and are not suitable for the '*on-demand'* treatment of emergency bleeds in Haemophilia-A.

Currently, only one brand is available in Indian market.

The CAT5: drug products are very different from the above CAT1: to CAT4: products, in as much as these are not the natural clotting factors, rather functional substitutes of their function/action. Since these are not true clotting Factor proteins, they are relatively free of the fearsome side effect of the development of '*inhibitors'* (per available data) seen in nearly 30% of haemophilia-A treated with CAT1 to CAT4 drug products. This translates into huge indirect cost benefits.

These CAT5: drug products mimics function of clotting Factor VIII with higher potency, and with very long half-life of 4-5 weeks which makes it possible to administer it only once in a month, and requiring minimal laboratory monitoring or titration with pharmacokinetics. Further, CAT5: products can be administered via a more tolerable and easier subcutaneous route. All this is immensely acceptable to patient and beneficial in saving on infrastructural costs for haemophilia-A treatment in India.

Efficacy of CAT5: drug products is similar, and the safety is better in terms of freedom from 'inhibitors.'

Haemophilia-A patients with inhibitors respond beautifully to CAT5: drug products, and which remains the drug of choice.

The CAT5:NFT-A products with their long-duration steady levels are the preferred choice for RRT in haemophilia-A. The real-world experience bears out the rapid switchovers to CAT5: drug products, globally and is expanding in India.

The CAT5: drug products have a history of the risk of life-threatening thrombotic complications, which after investigations were attributed to the concomitant use of CAT21: BPA product. Subsequent, advisory on this drug-drug interaction has largely ameliorated these side effects and these advisories now forms part of guidelines on using CAT5: drug products.

Another limitation of CAT5: drug products is that these are not recommended in managing emergency bleeds.

CAT5:NFT-A costing

The CAT5: drug products not only differ in their properties but are marketed in different units of measurement.

The cost and the issues in comparative costing of this 'non-factor' product against 'clotting factors' (the per unit IU cost is not applicable because it is available as mg). This requires innovative ways for evaluating bids for procurement and for fair playing field across the drug products for haemophilia-A.

Nevertheless, a patient-based costing is attempted below:

The Standard manufacturer prescribed RRT protocol using CAT5: NFT-A drug products is as under:

After an initial loading with 3 mg per kg body weight once weekly for the first 4 weeks, there are three options for the maintenance regimen:
a) 1.5 mg per kg body weight once in 1 week
b) 3 mg per kg body weight once in 2 weeks
c) 6 mg per kg body weight once in 4 weeks

The overall dose consumption or its costing remains the same across the three maintenance regimen for RRT in haemophilia-A.

Thus, for a Haemophilia-A patient weighing 10 Kg on 4-weekly RRT regimen requires CAT5: dose of:

6 mg x 10 x 1 = 60 mg per 4 weeks, or
60 x 30/28 = 65 mg per month

At indicative cost of Rs.1,401 per mg of one CAT5:NFT-A drug product, it translates into:
Rs. 84,060 per 4 weeks or
Rs.91,065 per month

The cost gets meaningfully reduced by 2/3rd under the formalised support programme from the manufacturer and which is available to all including Government institutions. Under this scheme, patient gets two vials free for every paid vial.

Adjusting for this, in the notional cost of CAT5: product comes to Rs.467 per mg. This translates into paid costing of :

Rs. 28.020 per 4 weeks or
Rs.30,355 per month

For other body weights, the above will apply in arithmetic proportion.

Indicative costs of these regimen are shown in comparative manner for haemophilia-A in the Table-2.

Thus, the cost is being made competitive from the manufacturer's offer of 2 free for 1 paid.

Also, this cost would be the same for RRT in haemophilia-A, irrespective of the absence or presence of inhibitors. Otherwise, the comparative costs for treating 'inhibitor' patients is dozens-fold. Hence in this sub=group, CAT5: drug products would remain the first choice.

Guidelines on parameters for selecting the drug products for prioritisation of haemophilia treatment are described in *Table 2a*, *2b*, and *Table 3*.

HAEMOPHILIA-B

The following CAT: drug products are available for treatment of Haemophilia-B, namely

1. CAT6: pdSHL-B
2. CAT8: rtSHL-B
3. CAT9: rtEHL-B

All drug products are clotting factor based.

CAT6:pdSHL- B drug products for Haemophilia- B

All the CAT6: pdSHL-B drug products can be used for both the *Regular Replacement Therapy* and the emergency 'on-demand' treatment of bleeds in haemophilia-B.

Only limited brand products under CAT6: are available in Indian market.

Their efficacy is proven, and safety has improved over time, though the concerns of unintended and unforeseen transfusion transmitted side effects remain.

As for the risk of development of 'inhibitor' Haemophilia-B to CAT6: drug products is much lower *vis-a-vis* haemophilia-A.

All the drug products under CAT6: are found similarly efficacious at standard doses, and as in the case of Haemophilia-A, attempts are made to conserve clotting Factor by using intermediate/ low-dose regimen. This needs more scientific validation.

CAT6: costing

Owing to the longer half-life of 18-24 hours, the dosing is less frequent for RRT with CAT6: drug products.

Indicative drug product posology for CAT6: range under different variants of RRT regimen is as under:

a) High- Dose regimen

40-60 IU per kg body weight, twice a week

b) Intermediate - Dose regimen

20-40 IU per kg body weight, twice a week

c) Low - Dose regimen

10-15 IU per kg body weight, twice or once a week

The higher dose regimen produce better results of haemophilia, but at an economic cost.

Thus, for Standard RRT protocol of twice weekly dosing, a Haemophilia-B patient weighing 10 Kg may require CAT1: dose of

RRT regimen

50 IU per Kg body weight twice in a week.

50 IU x 10 x 2 x 4 = 4,000 IU per 4 weeks, or

50 IU x 10 x 2/7 x 30 = 4,285 IU per month

At indicative cost of Rs.12 per IU of CAT6: pdSHL- B drug products, it comes to:
Rs. 48,000 per 4 weeks, or

Rs.51,428 month

To compare an RRT regimen in haemophilia-B using CAT6: drug products at 25 IU per Kg in patient weighing 10 Kg would be:

25 IU x 10 x 2 x 4 = 2,000 IU per 4 weeks, or
2,143 IU per month

with estimated cost at Rs.12 per IU for CAT6: drug products at
Rs. 24,000 per 4 weeks, or
Rs.25,714 month

Using these in '*off-label'* lower-dose or higher frequency RRT regimen will proportionately bring down the consumption and the costing.

With significantly better drug products under CAT9:, there is a trend to move away from CAT6: products (*vide infra*).

However, in the interest of hierarchy of Health Equity, it may necessitate procuring the cheaper CAT6: drug products in resource-constraint settings, and with inadequate availability of the EHL

Guidelines on parameters for selecting the drug products for prioritisation of haemophilia treatment are described in *Table 2a*, *2b*, and *Table 3*.

CAT8:rtSHL- B drug products for Haemophilia- B
All the CAT8:rtSHL- B drug products can be used for both the *Regular Replacement Therapy* and the emergency 'on-demand' treatment of bleeds in haemophilia-B.

Only one brand product is available in Indian market under CAT8:
It remains inadequate.

The efficacy of CAT8: drug products is proven and similar to CAT6: drug products, but for the safety concerns of unintended and unforeseen transfusion transmitted side effects from CAT6: products.

The risk of development of 'inhibitor' in haemophilia-B treated with CAT8: drug products is similar to that with CAT6: products.

There is likely to be increasing demand in favour of recombinant technology-based drug products to meet the escalating demands of haemophilia-B community, esp. with limited supply of safe blood plasma and the concerns therein.

<u>CAT8: costing</u>
The clinical posology of CAT8: drug products is similar to CAT6: products, with variant protocols of high/standard, intermediate or low-dose (*off label)*.

At standard dose of 50 IU per Kg body weight twice in a week for a 10 Kg body weight patient, the costing for CAT8: drug products works out to:

50 IU x 10 x 2 x 4 = 4,000 IU per 4 weeks, or

50 IU x 10 x 2/7 x 30 = 4,285 IU per month

At indicative cost of Rs.25 per IU of CAT8: drug product, it comes to:
Rs. 4000 x 25= 1,00,000 per 4 weeks, or
Rs. 1,07,125 per month

Comparing against an RRT regimen in haemophilia-B using CAT6: drug products at 25 IU per Kg in patient weighing 10 Kg would be:

25 IU x 10 x 2 x 4 = 2,000 IU per 4 weeks, or
2,143 IU per month

with estimated cost at Rs.25 per IU for CAT6: drug products at
Rs. 50,000 per 4 weeks, or
Rs.53,575 in a month

Guidelines on parameters for selecting the drug products for prioritisation of haemophilia treatment are described in *Table 2a*, *2b*, and *Table 3*.

CAT9:rtEHL- B drug products for Haemophilia- B

The CAT9: drug products can be used for both the *Regular Replacement Therapy* and for the 'on-demand' treatment of emergency bleeds in haemophilia-B.

Only a single brand product is available in Indian market under CAT9:

There are biological advantages of extending half-life of clotting Factors, and this excels when it comes to CAT9: drug products for haemophilia-B, where it goes up to x5 times its own SHL products.

This longer half-life brings enormous benefits to CAT9: drug products for Haemophilia- B patients by reducing the frequency of intravenous injections down to once in a week or even 10 days- a reduction of up to 70%.

Also, the pharmacokinetics of CAT9: drug products provides higher trough levels of clotting Factor IX, sustained for longer period, which translates into lower bleed rates and higher efficacy

Treatment can be personalised with PK-driven protocol, resulting in optimisation of drug usage including surgeries and the clinical outcome. and the cost optimisation.

As with other drug products for Haemophilia-B treatment, the risk of 'inhibitor' development remains low with the CAT9: drug products.

With better adherence by patient from fewer injections, better efficacy from improved bleed control and better Quality of Life, most patients with Haemophilia-B without 'inhibitors' can aspire for these benefits associated with CAT9: drug products.

For centres with institution-based treatment (not home therapy), the institutions and other would save on time, space and infrastructure costs compared to CAT6: or CAT8: drug products.

The CAT9: drug products deserve serious consideration for all haemophilia-B.

CAT9: costing

The prescribed RRT regimen for haemophilia-B using CAT9:rtEHL-A drug products is

40 IU per Kg body weight once in a week

Thus, a Haemophilia-B patient weighing 10 Kg on the prescribed RRT with CAT9: drug products would require:

40 IU x 10 x 4 = 1600 IU per 4 weeks, or
40 IU x 10 x 30/7 = 1,715 IU per month

At indicative cost of Rs.40 per IU of CAT9: drug product, it translates into:
Rs. 64,000 per 4 weeks, or
Rs.68,570 per month

A low dose protocol may administer it once in 10 days to save on costs.

Further, the indirect shadow infrastructural costs add to savings, and these tend to be significantly much higher in the current set ups in India.

Using these *'off-label'* lower-dose (*vide supra*) or higher duration RRT regimen will proportionately bring down the costing.

The costs of the recombinant drug products are likely to come down with time.

Guidelines on parameters for selecting the drug products for prioritisation of haemophilia treatment are described in *Table 2a*, *2b*, and *Table 3*.

XI. Framework Need for providing Haemophilia Care by the State

In India, haemophilia care remains largely the responsibility of the State.

Every patient with haemophilia deserves health equity and access to adequate treatment for haemophilia as per Standard of care. The treatment has huge benefits in normalising the life. However, these can accrue only when the treatment is started as early as possible in early childhood years when they are still dependent and have to be protected. Also, it is cheaper to provide treatment during that period.

Regular Replacement Therapy (RRT) is expensive and should not be distributed in fragmented manner by the State when their resources are limited. A prioritization may be warranted, based on needs, the cost-benefit ratios, and the likely future contributions to the life and economy of self, the family, the society and the nation.

The following list of parameters is based on our 15-year experience with haemophilia in India and due deliberations including a dedicated national level *Haemophilia Conclave 2023- Policy, Protocols & Roadmap to haemophilia care in India,* combining with a Delhi technique.

The following *Action Tables 2 and 3* summarise the parameters and the processes- the first for prioritising RRT in Haemophilia-A followed by the other for Haemophilia-B.

These guidelines may be adopted/ modified/ expanded/ deleted to adapt to the local prevailing needs and circumstances, including the weightage to be assigned to a given parameter.

NOTE: For '*Episodic'* or '*On-Demand'* treatment of emergency bleeds, no patient with haemophilia shall be denied treatment anywhere.

XII. Action Tables for Decision Making In Haemophilia-A RRT

We have developed some *Action Tables* to collate the parameters that go in decision making. Besides the scientific evidence, these incorporate the real-world experience with a Delhi consensus.

These are evolving and wider use and feedback and time will give more strength to these *Action Tables 2 and Table 3* for Haemophilia-A and Haemophilia-B, respectively.

For the Haemophilia- A treatment related policy/ protocols, the drug product are broadly stratified on the sub-group it belongs to:

i) *Clotting Factor Therapy* (CFT)
ii) *Non-clotting factor Therapy* (NFT)

This is the criterion for bifurcating *Table 2* for haemophilia-A into the *Table 2a* and *Table 2b*.

Further, remember to assign and consider any given drug product belonging to a category CAT: number as detailed above.

These two *Table 2a* and *Table 2b* provide summary guidelines on evaluating the parameters in decision making.

Table 2a relate to the drug products belonging to *Clotting Factor Therapy* sub-group, under the *CAT1*:pd SHL-A, *CAT3*: rt SHL-A, and *CAT4*: rt EHL-A.

whereas *Table 2b* relate to the drug products belonging to the *Non-clotting Factor Therapy*, under *CAT5*:NFT-A.

It may simplify to first work out on the *Table 2b*, which has only one CAT5: albeit important priority. This may make the decision-making process on the several *Clotting Factor* drug products under different CAT: number simpler and logical.

HAEMOPHILIA-A (CFT)

Action Table 2a

Decision making forprioritising haemophilia-A drug products,*CFT* sub-group*

(*CAT1*:, *CAT3*:, and *CAT4*:)

S. No.	Parameter	Weighted Score (indicative)	Choose as applicable from *'Parameter'*	Choose as applicable *'Weighted Score'*
A.	NON-HAEMOPHILIA PARAMETERS			
1.	Family Income category, a) BPL b) Non-BPL	 3 1		
2.	Nearest access to govt. haemophilia treatment facility in his State of residence a) Over 50 Kms b) 31-50 Kms c) 11-30 Kms d) Under 10 Kms	 4 3 2 1		
3.	Family support a) No living parent, No sibs b) No living parent, Has sibs c) Only one living parent d) Both parents alive	 4 3 2 1		
4.	Age (completed years) a) upto 5 years b) 06- 10 years c) 11- 18 years d) 19 – 26 years e) over 26 years	 5 4 3 2 1		
		SUB-TOTAL SCORE (A)		
B.	HAEMOPHILIA RELATED PARAMETERS			
5.	ABR more than 12	1		
6.	"Serious-site" bleeds**	1		
7.	Presence of Target joint(s)	1		
8.	Absence of known Inhibitors to clotting Factor VIII	2		
9.	Competency in self-infusing the clotting factor	1		
10.	BMI under 30***	1		
11.	Student	1		

12.	Working but employer does not provide for hemophilia treatment	1		
13.	No other insurance (private) covers hemophilia treatment	1		
			SUB-TOTAL SCORE (B)	
			TOTAL SCORE (A + B)	

* Treatment spectrum includes all protocols - including primary, secondary, and tertiary RRT
** "serious-site bleeds such as intracranial bleed, intra-abdominal, intrathoracic bleed, pseudotumours
*** Body weight in Kg (W), and Height in Metres (H), then BMI = W/H^2

NOTE: The indicative Weighted Score in this Table may be modified based on local *milieu* and needs

SCORING and PRIORITISATION:

The likely scores will range as under:

- Total Score (A+B) is likely to range from 5 to 26
- Sub Score (A) is likely to range from 4 to 16
- Sub Score (B) is likely to range from 1 to 10

i) Treatment Priority, based on Sub-Score A non-haemophilia parameters

Sub-Score A score		**Treatment Priority**
More than 11		++++ Priority
Score 8-11		+++ Priority
Less than 8		++ Priority

ii) Drug product CAT: priority, based on Sub-Score B haemophilia-related parameters

Sub-Score B score	**Drug product CAT: Priority**		
	1st choice	2nd choice	3rd choice
More than 6	CAT4:	CAT3:	CAT1:
Score 5-7	CAT3:	CAT4:	CAT1:
Less than 5	CAT1:	CAT3:	CAT3:

NOTE:
i) In a given sub-group, priority may be further refined based on actual score in the given sub-group score
ii) If patient has significant persistent Inhibitors, go to Table 2b for further assessment

HAEMOPHILIA-A(NFT)

Action Table 2b

Decision making for haemophilia-A drug products, belonging to *NFT* sub-group*

(*CAT5:*)

S. No.	Parameter	Weighted Score (indicative)	Choose as applicable from *'Parameter'*	Choose as applicable *'Weighted Score'*
A.	NON-HAEMOPHILIA PARAMETERS			
1.	Family Income category, a) BPL b) Non-BPL	 3 1		
2.	Nearest access to govt. haemophilia treatment facility in his State of residence a) Over 50 Kms b) 31-50 Kms c) 11-30 Kms d) Under 10 Kms	 4 3 2 1		
3.	Family support a) No living parent, No sibs b) No living parent, has sibs c) Only one living parent d) Both parents alive	 4 3 2 1		
4.	Age (completed years) a) upto 5 years b) 06- 10 years c) 11- 18 years d) 19 – 26 years e) over 26 years	 5 4 3 2 1		
		SUB-TOTAL SCORE (A)		
B.	HAEMOPHILIA RELATED PARAMETERS			
5.	ABR more than 12	1		
6.	"Serious-site" bleeds**	1		
7.	Presence of Target joint(s)	1		
8.	Presence of persistent Inhibitors to clotting Factor VIII	7		
9.	BMI under 30***	1		
10.	Student	1		
11.	Working but employer does not cover hemophilia RRT	1		

12.	No other insurance (private) covers hemophilia RRT	1		
			SUB-TOTAL SCORE (B)	
			TOTAL SCORE (A + B)	

* Treatment spectrum includes all protocols - including primary, secondary, and tertiary RRT
Not recommended for '*Episodic'* or '*On-Demand'* situation bleeds
** "serious-site bleeds such as intracranial bleed, intra-abdominal, intrathoracic bleed, pseudotumours
*** Body weight in Kg (W), and Height in Metres (H), then BMI = W/H^2
NOTE: The indicative Weighted Score in this Table may be modified based on local *milieu* and needs

SCORING and PRIORITISATION:

The likely scores will range as under:

- Total Score (A+B) is likely to range from 5 to 30
- Sub Score (A) is likely to range from 4 to 16
- Sub Score (B) is likely to range from 1 to 14

i) Treatment Priority, based on Sub-Score A non-haemophilia parameters

Sub-Score A score		**Treatment Priority**
More than 11		++++ Priority
Score 8-11		+++ Priority
Less than 8		++ Priority

ii) Drug product CAT: priority, based on Sub-Score B haemophilia-related parameters

Sub-Score B score	**Drug product CAT: Priority**		
	1st choice	2nd choice	3rd choice
More than 7	CAT5:	CAT5:	CAT5:
Less than 8	see *Note* below	see *Note* below	see *Note* below

NOTE:
i) In a given sub-group, priority may be further refined based on actual score in the given sub-group score
ii) All patients with Sub-score B score of more than 7 to qualify for CAT:5 drug products
iii) All patients with Sub-score B score of less than 8 and with Sub-score A score of more than tento qualify for CAT:5 drug products
iv) All patients with Sub-score B score of less than 8, and with haemophilia parameter at serial 6-7[#], in *Table 2b* may also qualify for CAT:5 drug products.
(6-7[#] serious-site bleeds or target joint)

HAEMOPHILIA-B

Action Table 3

Decision making for prioritising haemophilia-B drug products, *CFT* sub-group*

(CAT6:, CAT8:, CAT9:)

S. No.	Parameter	Weighted Score (indicative)	Choose as applicable from *'Parameter'*	Choose as applicable *'Weighted Score'*
A.	NON-HAEMOPHILIA PARAMETERS			
1.	Family Income category, a) BPL b) Non-BPL	 3 1		
2.	Nearest access to govt. haemophilia treatment facility in his State of residence a) Over 50 Kms b) 31-50 Kms c) 11-30 Kms d) Under 10 Kms	 4 3 2 1		
3.	Family support a) No living parent, No sibs b) No living parent, Has sibs c) Only one living parent d) Both parents alive	 4 3 2 1		
4.	Age (completed years) a) upto 5 years b) 06- 10 years c) 11- 18 years d) 19 – 26 years e) over 26 years	 5 4 3 2 1		
		SUB-TOTAL SCORE (A)		
B.	HAEMOPHILIA RELATED PARAMETERS			
5.	ABR more than 12	1		
6.	"Serious-site" bleeds**	1		
7.	Presence of Target joint(s)	1		
8.	Absence of known Inhibitors to clotting Factor IX	2		
9.	Competency in self-infusing the clotting factor	1		
10.	BMI under 30***	1		
11.	Student	1		

12.	Working but employer does not provide for hemophilia treatment	1		
13.	No other insurance (private) covers hemophilia treatment	1		
			SUB-TOTAL SCORE (B)	
			TOTAL SCORE (A + B)	

* Treatment spectrum includes all protocols - including primary, secondary, and tertiary RRT
** "serious-site bleeds such as intracranial bleed, intra-abdominal, intrathoracic bleed, pseudotumours
*** Body weight in Kg (W), and Height in Metres (H), then BMI = W/H^2

NOTE: The indicative Weighted Score in this Table may be modified based on local *milieu* and needs

SCORING and PRIORITISATION:

The likely scores will range as under:

- Total Score (A+B) is likely to range from 5 to 26
- Sub Score (A) is likely to range from 4 to 16
- Sub Score (B) is likely to range from 1 to 10

i) Treatment Priority, based on Sub-Score A non-haemophilia parameters

Sub-Score A score		**Treatment Priority**
More than 11		++++ Priority
Score 8-11		+++ Priority
Fewer than 8		++ Priority

ii) Drug product CAT: priority, based on Sub-Score B haemophilia-related parameters

Sub-Score B score	**Drug product CAT: Priority**		
	1st choice	2nd choice	3rd choice
More than 6	CAT9:	CAT8:	CAT6:
Score 5-7	CAT9:	CAT8:	CAT6:
Fewer than 5	CAT9:	CAT8:	CAT6:

NOTE: In a given sub-group, priority may be further refined based on actual score in the given sub-group score

SUMMARY

First National Consensus Recommendations on Haemophilia Treatment from the National Experts of Our Country

Haemophilia is a rare genetic disease, disastrous outcome without treatment.

The treatment benefits unparalleled and unsurpassable, by bringing quality of life back to these children and making them a proud productive citizen like any other. The small number of patients work to provide treatment to all.

This requires identifying them when they are young, diagnosing and providing appropriate treatment.

Pursuant to scientific research, the drug products for treatment of haemophilia have expanded in big manner over the past two decades.

This expanded armamentarium of drug products has come with anxieties and uncertainties across the stakeholders from the patient himself to the treaters and administrators and policy makers.

The myriad drug products have their nuances and individual roles in individual haemophilia.

There was a felt need for a document to guide on recommendation for selecting the optimal drug products from the lot, for individual patients and with local constraints.

The current document ***HHCN Recommendations on Policy & Protocols for selecting the right product for Optimal haemophilia care in India*** attempts to fill this gap.

These *Haemophilia & Health Collective of North®* recommendations have attempted to provide and simply the process for selecting the right drug product for Haemophilia:

a) Basic understanding of the disease haemophilia
b) Drug treatment and posology for haemophilia treatment
c) Drug products available for haemophilia treatment
d) Pros and cons of individual drug product
e) Simplifying the complex and confusing medical names of drug products, by Categorising them in under stable manner and ease of decision making
f) Difficulties in making comparative choice based on orthodox bidding process
g) Moving from per unit bidding to per month/ annual treatment
h) Direct and indirect costing benefits
i) Costing and cost effectiveness of different drug products for haemophilia
j) Action Tables for Final decision making in making the right choice

Each of the above segment has been described under separate sections, and one can easily move from one to any other.

The hallmark of this document is simplifying the understanding of and comprehending the large number of drug products under an innovative framework of assigning unique CAT: numbers to refer to drug products; and the final *Action Tables* to assist in decision making.

Pray this initiative proves useful
With Best Wishes
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