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REVIEW ARTICLE

Clinical phenotype of severe and moderate haemophilia: Who should receive prophylaxis and what is the target trough level?

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Abstract

Introduction: One of the most often stated tenets of haemophilia care is that prophylaxis converts a person from a severe to a moderate phenotype. In this review, we argue that this is not an accurate assumption and that people on prophylaxis predominantly have factor VIII/IX levels in the mild range.

Moderate haemophilia and prophylaxis: People with moderate haemophilia, who are treating with on-demand regimens, experience joint bleeds and often develop significant arthropathy. This is especially true for people with a baseline level of 1–3 IU/dl, as first reported 55 years ago, and confirmed in more recent studies. Evidence is emerging suggesting that people with severe haemophilia who are using prophylaxis have better musculoskeletal outcomes than people with moderate haemophilia treated episodically.

Trough levels: The debate around the optimum trough level whilst on prophylaxis is ongoing. It is not appropriate to extrapolate information about baseline levels to recommendations about target trough levels on prophylaxis because these are different situations. Studies are emerging that support higher target trough levels than previously used, but in spite of this, the aim of achieving zero bleeds remains elusive with both factor replacement and non-replacement therapies.

Conclusions: We recommend that people with moderate haemophilia, especially those with a baseline of 1–3 IU/dl, should be offered prophylaxis based on the same criteria as people with severe haemophilia. Trough levels should be maintained above 3 IU/dl or higher if a level of 3 IU/dl does not control breakthrough bleeding and prophylaxis should be tailored to the bleeding phenotype. This advice is in line with recently published guidelines from the World Federation of Haemophilia and the UK Haemophilia Centre Doctors' Organisation.

KEYWORDS
arthropathy, haemophilia, moderate, prophylaxis, trough level

1 | INTRODUCTION

Primary prophylaxis, with factor (F)VIII or FIX, is the recommended standard of care for young children with severe haemophilia. The aim of prophylaxis is to prevent bleeding episodes, especially haemarthroses, with the long-term goal that the child reaches maturity with a normal musculoskeletal system. Prophylaxis is recommended to continue life-long.[1–4] In older people with haemophilia (PwH), secondary or tertiary prophylaxis is used to reduce bleeding episodes, limit progression of arthropathy and improve mobility.[5–7] Long-term studies support the efficacy of primary prophylaxis for preventing arthropathy in the large majority of children with severe haemophilia.[8,9] However, delay in either starting prophylaxis or escalating to full dose is associated with musculoskeletal complications.[10–12] Therefore, guidelines advocate initiating prophylaxis before or at the time of the first joint bleed. In line with guidelines, we recommend escalating prophylaxis rapidly to full dose and continuing this treatment life-long[1,2] although some clinicians escalate prophylaxis based on the pattern of bleeding.

Although the severity and progression of arthropathy are associated with the number of bleeds into a joint, this relationship is not always apparent and abnormalities can be demonstrated on magnetic resonance imaging (MRI) in joints with no recorded bleeds.[9] This observation is attributed to subclinical bleeding, and whilst this is a plausible hypothesis, definitive evidence to confirm the assumption is awaited. The concept of subclinical bleeds contributes to the debate over whether trough levels higher than 1 IU/dl would reduce arthropathy by decreasing minor and unrecognised bleeding episodes.

2 | SEVERE VERSUS MODERATE HAEMOPHILIA

One of the most commonly stated tenets of haemophilia care is that prophylaxis converts the disorder from a severe to a moderate phenotype. This assumption is based, in part, on the original concept for prophylaxis which was to maintain a trough FVIII/IX above 1 IU/dl, in the range of moderate haemophilia.[13] However, a comparison of the levels of FVIII/IX experienced by a person with severe haemophilia on prophylaxis and a person with moderate haemophilia treated on-demand shows that these are very different scenarios (Figure 1). In moderate haemophilia, the baseline level of FVIII is consistently low throughout the week. This means that the individual has no peaks of FVIII/FIX at the time of potential trauma or physical activity and so will not benefit from the additional protection that this would afford. In contrast, a person with severe haemophilia on prophylaxis can tailor infusions so that they have normal FVIII/IX levels at the time of predictable haemostatic challenges and personalisation of care is routine practice for many people.[14,15] It is important to recognise that, in mild and moderate haemophilia A, stress or trauma can increase the baseline factor VIII and afford a temporary increased level of protection. This is not the case in haemophilia B.

A person on standard prophylaxis would expect to have a FVIII level above 5 IU/dl most of the time with levels only falling into the moderate range during the latter part of the second day and night. For example, in severe haemophilia treated with an infusion of 30 IU/kg on alternate days using a FVIII concentrate that has a half-life of about 12 h one would expect to spend more than 50% of the time with a level above 5 IU/dl. If treatment was with 15 IU/kg daily, to have more regular peaks, then FVIII would be above 5 IU/dl for more than 85% of the time. In contrast, moderate haemophilia treated on-demand will be associated with a FVIII/IX level below 5 IU/dl for prolong periods of time and higher levels will occur only at the times of intermittent treatment or minor increases seen at the time of stress. In effect, therefore, prophylaxis converts severe haemophilia to mild rather than moderate haemophilia for significant amounts of time and results in FVIII/FIX levels substantially higher than 5 IU/dl for most of the week. Indeed, a person with moderate haemophilia who has a baseline of 1 IU/dl will have lower FVIII/FIX levels than a person with severe haemophilia on prophylaxis at all times except when treating a bleed.

In most haemophilia centres, prophylaxis is more likely to the offered for severe haemophilia than for moderate. The reasons for this are complex but may relate to the assumption that moderate haemophilia protects against arthropathy in a similar way to prophylaxis in severe haemophilia. If moderate haemophilia was phenotypically

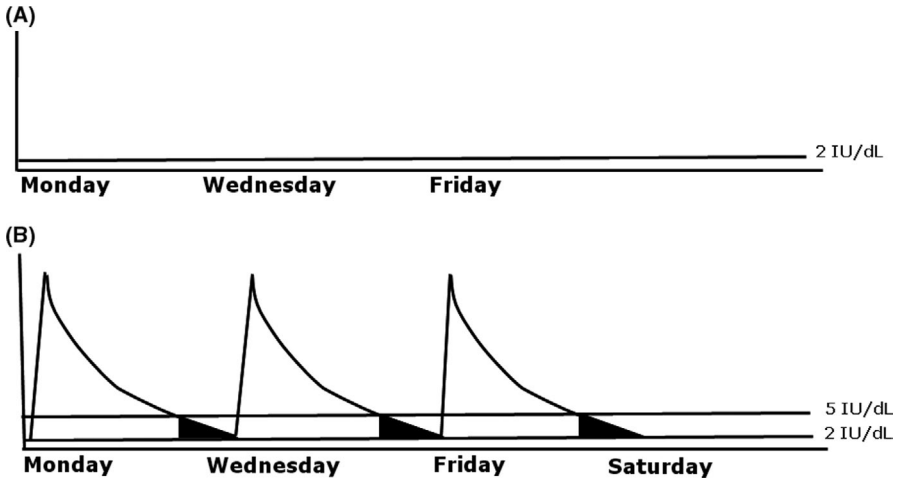

FIGURE 1 Factor levels in moderate haemophilia and severe haemophilia on prophylaxis with trough level at 2 IU/dl. Schematic representation of the time spent at different factor levels comparing (A) moderate haemophilia treated episodically and (B) severe haemophilia on prophylaxis. At all times, the person with severe haemophilia has higher factor levels and spends the majority of time with a level in the mild range. The *y*-axis is arbitrary

similar to severe haemophilia on prophylaxis, arthropathy should be uncommon and annualised bleed rates (ABR) should be low. This assumption, however, is not correct and this has been known for more than 50 years. A seminal paper published in 1965 described the experience of haemophilia care in Sweden before coagulation factor concentrates were routinely available.[13] People with a baseline FVIII/IX <1 IU/dl had median (IQR) joint score of 12 (9-16) demonstrating significant arthropathy. Importantly, people with a baseline FVIII/IX levels 1–3 IU/dl also had abnormal joint scores with a median (IQR) 8, (6-11) demonstrating that this level of FVIII/IX was not protective against arthropathy. If the baseline FVIII/IX was >3 IU/dl, the joint score was zero in all but one case (Figure 2). It is important to note, however, that the joint scoring system used in this study was relatively insensitive and so would not have identified less severe joint pathology. This finding has been replicated recently in a cohort of people with haemophilia in Pakistan who had minimal access to FVIII concentrate. At an average age of 16 years, the Haemophilia Joint Health Score (HJHS) was median (IQR) 24 (16–48) in severe haemophilia and 18 (5–30) in the moderate group.[16] It is clear that moderate haemophilia, in people who do not have access to coagulation factor concentrates, is not protective against arthropathy.

This raises the question of whether people with moderate haemophilia who have access to FVIII/IX would be protected against arthropathy because early treatment of bleeds might prevent synovitis and inflammatory changes. This question was addressed in a UK Haemophilia Centre Doctors' Organisation (UKHCDO) investigation of the long-term joint outcomes of people registered on the UK National Haemophilia Database. The moderate haemophilia group had a median (IQR) baseline FVIII level of 2 (1-3) IU/dl and so were at the lower end of the moderate range. In the group born between

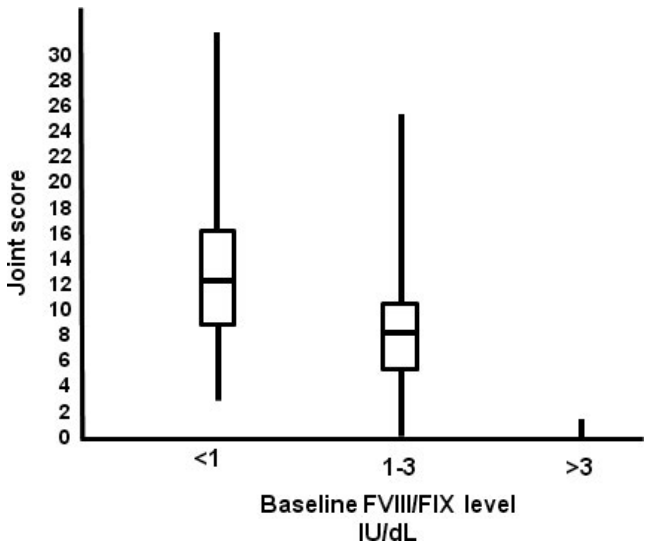

FIGURE 2 Haemophilic arthropathy in people with haemophilia reported in Sweden in 1965. Box plots are derived from data available in Ahlberg[13] figure 17 page 33. In the group >3 IU/dl, one person had a joint score of 3 and in all others the score was zero. The joint score used was not sensitive to soft tissue changes, and the results cannot be compared to HJHS

1976 and 1996, the HJHS was found to be increased to a similar level in people with both severe and moderate haemophilia, irrespective of whether they were being treated on-demand or with tertiary prophylaxis.[17] This study confirmed findings in the Netherlands where it was shown that by the age of 40 years, moderate haemophilia was associated with a median HJHS of 8 if the FVIII was ≤2 IU/dl or the first joint bleed had occurred before the age of 5 years, and in this group, 25% of people had a joint score >12. Even those with FVIII >2 IU/dl or with a first haemarthrosis after the age of 5 years, 25% had a joint score of ≥8.[18] These studies demonstrate that access to FVIII concentrate does not prevent arthropathy in moderate haemophilia and that by middle age joint pathology is common.

In the UKHCDO study, children with severe haemophilia born between 1996 and 2015, when prophylaxis was routine care in the UK, had a median (IQR) HJHS of 0 (0–1) demonstrating excellent outcomes across all UK haemophilia centres.[17] This finding relates to a time when UK practice was to initiate prophylaxis at the latest after the first joint bleed and to maintain a trough FVIII level of about 1 IU/dl or higher if breakthrough bleeds occurred.[3] In contrast, children with moderate haemophilia born during the same period of time had a median (IQR) HJHS of 3 (0–9) demonstrating significant arthropathy in more than 25% of children.[17] The reason for the higher HJHS in children with moderate haemophilia cannot be known for certain but a plausible explanation is that they started prophylaxis later, and possibly less intensively, than the severe cohort, potentially because there was an assumption that they would be less prone to developing arthropathy. In addition, it is possible that subclinical bleeds may have affected children with moderate haemophilia more than those with severe haemophilia on prophylaxis, who would experience a peak level every other day, and this may have contributed to the joint damage. It appears that people with moderate haemophilia need to experience more bleeds than those with severe haemophilia and, in some cases, need to develop evidence of arthropathy before they have the opportunity to receive prophylaxis.

The pattern of bleeding in people with different severities of haemophilia was addressed in a study designed to investigate whether the traditional classification of the severity of haemophilia remained relevant.[19] The authors questioned whether the approach to severe and moderate haemophilia (early prophylaxis and close monitoring versus mainly on-demand and monitored less often) was justified. The group reported that people with moderate haemophilia and a baseline FVIII level of 1–2 IU/dl had a median annualised joint bleed rate (AJBR) of about 5.5, despite 35% being on prophylaxis. As the baseline level increased from 2 to 3 IU/dl, the AJBR fell rapidly to about 2 and between 3 and 5, and there is a further decline to an AJBR of about 1. The AJBR did not approach zero until the baseline level reached 12 IU/dl. The AJBR for severe haemophilia could not be assessed in the study because >90% of this group were taking prophylactic treatment; however, it is known that people with severe haemophilia who are not on prophylaxis often experience more than 20 bleeds a year.[20,21] These data show that moderate haemophilia, especially with a baseline FVIII level between 1 and 3 IU/dl, is

associated with a significant number of joint bleeds each year and it is not surprising, therefore, that progressive arthropathy is seen.[17–19]

These studies demonstrate that the definition of moderate haemophilia encompasses a wide range of bleeding phenotypes and people with a baseline level of 1–3 IU/dl have a different pattern of bleeding and joint scores to those with levels 3–5 IU/dl. This was also seen in the joint scores in the early experience from Sweden (Figure 2).[13] This suggests that a classification of moderate haemophilia that spans 1–5 IU/dl might be too broad and potentially leads to a tendency to underestimate the severity of haemophilia in people are at the lower end of the moderate range.

3 | WHO SHOULD BE OFFERED PROPHYLAXIS?

In our opinion, the conclusion to be drawn from these data is that people with moderate haemophilia, and especially those with baseline levels between 1 and 3 IU/dl, should be offered prophylaxis if they experience any joint or other clinically significant bleeds. This was also the conclusion reached by a Dutch group who summed up by stating 'treatment decisions, such as starting prophylaxis, should therefore be tailored according to bleeding pattern rather than .... residual clotting factor levels'.[19] UKHCDO has recently revised its prophylaxis guidelines and now recommends that children with moderate haemophilia and baseline levels between 1 and 3 IU/dl should be considered for primary prophylaxis and that all people with haemophilia, irrespective of baseline FVIII/IX, should be considered for prophylaxis after the first joint bleed to reduce the risk of developing arthropathy.[2] This recommendation is also made by the World Federation of Haemophilia in their recently updated guidelines 'Prophylaxis is the standard treatment for many people with haemophilia, not only those with severe disease but also those with moderate deficiency, irrespectively of the hemophilia type, ideally initiated before any bleeding episode'. (https://onlinelibrary.wiley.com/doi/epdf/10.1111/hae.14046) and in a supporting editorial.[22]

The target trough level for prophylaxis in moderate haemophilia is not known, and it seems illogical to aim for a higher trough than in severe haemophilia. The risk of break through bleeds is associated with time spent at low levels rather trough level[23] and so returning to a baseline of 3 IU/dl for short periods of time may not be a significant risk. This question will need to be addressed as experience with prophylaxis in moderate haemophilia increases.

In addition, we recommend that moderate haemophilia should be followed up by specialist physiotherapists in the same way and with the same frequency as severe haemophilia. This is especially important in young children so that subtle signs of arthropathy can be detected even if overt clinical bleeds have not been reported. Children with moderate haemophilia who have signs of joint pathology should be offered prophylaxis.

4 | WHAT TROUGH LEVELS ARE REQUIRED DURING PROPHYLAXIS?

It is important not to confuse baseline FVIII/IX levels with trough levels on prophylaxis because these are very different measures. A paper investigating baseline levels[19] has been used to argue in favour of aiming for trough levels on prophylaxis of about 12 IU/dl; however, it is not justified to extrapolate data derived from baseline

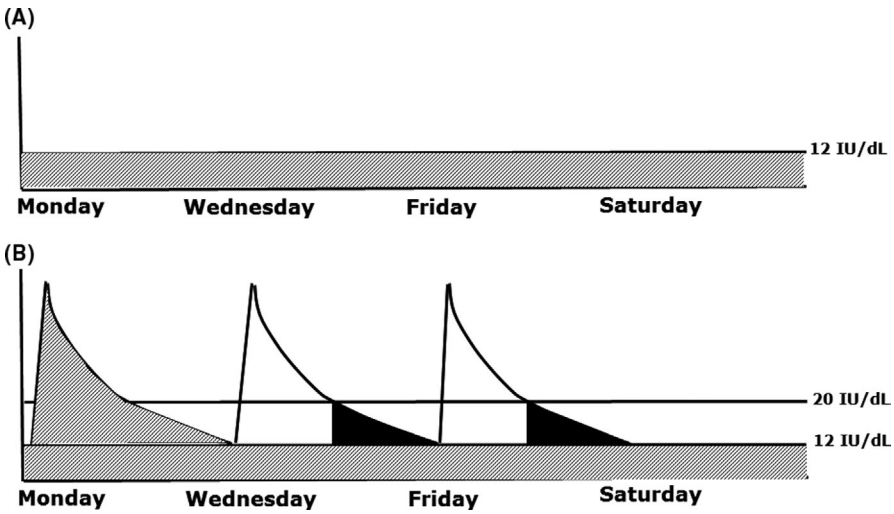

FIGURE 3 Factor levels in mild haemophilia and severe haemophilia on prophylaxis with trough level at 12 IU/dl. Schematic representation of the time spent at different factor levels comparing (A) mild haemophilia with a baseline level of 12 IU/dl treated episodically and (B) severe haemophilia on prophylaxis with a target trough level of 12 IU/dl. At all times, the person with severe haemophilia has a higher level and spends the majority of time with a level above 20 IU/dl. Scenario (A) is similar to the situation with Emicizumab and gene therapy achieving a level of 12 IU/dl. The difference in area under the curve comparing scenario a and b can be seen in the shaded areas for the time above 12 IU/dl plus the first treatment and the time between 20 and 12 IU/dl shown in black for the second two treatments. The area under the curve is substantially higher for the prophylaxis scenario. The *y*-axis is arbitrary

FVIII levels in this way and the authors did not draw this conclusion. A baseline of 12 IU/dl and a trough of 12 IU/dl are different as shown in Figure 3, and this difference is emphasised further when FVIII/IX area under curve (AUC) is considered. A baseline of 12 IU/dl has an AUC of 12 times 168 h whereas as a prophylaxis with a trough of 12 IU/dl has this minimum AUC plus that associated with the higher levels. If a trough level of 12 IU/dl was targeted, the individual would spend a substantial amount of time with their FVIII/IX above 20 IU/dl. It is important to recognise that a baseline FVIII of 12 IU/dl is likely also to increase at the time of stress or trauma and increase the AUC. To inform decisions about appropriate target trough levels on prophylaxis, studies that investigate this question directly are required.

Valentino et al used pharmacokinetic-guided dosing to target a trough FVIII level of 1 IU/dl and compared this to 'standard prophylaxis' of 20–40 IU/kg on alternate days. The target trough FVIII level of 1 IU/dl was successful achieved in the PK-guided arm and the median trough FVIII in the standard care arm was 3 IU/dl. The median ABR (IQR) was 2 (0–4.9) in the PK-guided arm and 1 (0–2.5) in the standard arm (p = 0.15), hinting that a trough of 3 IU/dl may give marginally better protection against bleeding than a trough of 1 IU/dl.[24]. In the pivotal study of rFVIII-Fc, one arm individualised dosing to achieve a trough level of at least 1–3 IU/dl. The mean (negative binomial 95% CI) ABR in that arm was 2.9 (2.3–3.7), but there was no control group to compare with.[20]

The only study that directly compares two target trough levels is the PROPEL study. This study used pharmacokinetic-guided dosing with a pegylated rFVIII to target trough levels of 1–3 or 8–12 IU/dl. The target trough levels were achieved, and in the 1–3 IU/dl group, the mean (Poisson's SD) of all bleed ABR was 3.6 (7.5) compared to 1.6 (3.4) in the 8–12 IU/dl arm. More people had zero bleeds in 6 months in the 8–12 IU/dl group compared to the 1–3 IU/dl group, 62% vs. 42%, but this was not statistically significant (p = .055). In a subgroup analysis of people who were able to follow the protocol closely, the proportion of people with zero bleeds was 67% and 40% in the 8–12 and 1–3 IU/dl groups, respectively (p = .02).[25] A post hoc analysis of another study suggested that most benefit in reducing the ABR on prophylaxis was derived by increasing the FVIII level to between 1 and 3 IU/dl but higher levels were required to achieve zero bleeds.[26]

A study of pegylated FIX randomised people with haemophilia B and a baseline FIX ≤2 IU/dl to on-demand treatment or weekly infusions of 10 IU/kg or 40 IU/kg. The participants were blinded to the dose of FIX and so would not have been influenced by this when reporting bleeds. The average trough levels achieved were 8.5 and 27.3 IU/dl in the 10 and 40 IU/kg arms, respectively. The all bleed ABR was median (IQR) 15.6 (9.6–26.5) in the on-demand group and 2.9 (1.0–6.0) and 1.0 (0.0–4.0) in the 10 and 40 IU/kg arms, respectively. Although this was not a study that targeted a specific trough level, it gives some indication of the ABR achievable with this product at two different trough levels compared to on-demand treatment.[27]

Achieving a trough FVIII level of 12 IU/dl may not be feasible in some cases, even using enhanced half-life FVIII products. Adherence and venous access issues may influence this. In the PROPEL study, some subjects needed to infuse daily to achieve a trough of 12 IU/dl and not all subjects could adhere to the regimen. The difference between clinical studies and real life needs to be considered. Achieving troughs of 12 IU/dl is much more feasible with enhanced half-life FIX.

Overall, these data support the view that higher trough levels are associated with fewer bleeds although it appears to be difficult to achieve an ABR of zero even with very high troughs. It must be recognised that bleed rates are patient reported and there is the potential for misclassification of events, especially if the person has significant arthropathy. Tailoring the trough level to minimise bleeding in individuals continues to be the practice of choice. Revised UKHCDO guidelines recommend aiming for a trough level of at least 3 IU/dl or higher if necessary to prevent bleeding.[2]

5 | TREATMENT WITH NON-COAGULATION FACTOR REPLACEMENT THERAPIES

Although comparing ABRs at various FVIII/FIX baseline levels with those associated with trough levels on prophylaxis is not comparing like with like, the situation with other treatment strategies is different. Emicizumab is associated with a constant level of haemostatic cover[28] and so is more analogous to the baseline situation described by den Uijl and colleagues.[19] This is also the case for other treatment strategies that are undergoing clinical trials such as inhibition or suppression of inhibitors of coagulation[29] and gene therapy.[30,31]

In the HAVEN 3 study, emicizumab was associated with a median (IQR) ABR of 1.5 (0–4.3) in people who had been taking prophylaxis previously. Achieving zero bleeds remained challenging with 55.6% (95% CI 42.5–68.1) reaching this target, similar to that achieved in the 10–12 IU/dl FVIII trough arm of the PROPEL study.[25] The study reports a treated bleed ABR of 1.5 (95% CI, 0.9–2.5) and 1.3 (0.8–2.3) in the once a week and once every 2 weeks emicizumab arms, respectively, compared to 38.2 (22.9–63.8) in the no prophylaxis group.[28] This result is similar to those achieved with FVIII/FIX replacement at higher trough levels.

In an open-label observational study of antithrombin suppression with fitusiran published in abstract form, the ABR was 1.0 for both inhibitor and non-inhibitor groups. The outcomes of the phase 3 trial are awaited, but these early results are similar to those achieved by emicizumab and FVIII/FIX aiming for higher trough levels. In a gene therapy study of severe haemophilia A, the treated bleed rate approached zero at a FVIII level of about 12–15 IU/dl,[30] very similar to the findings of den Uijl et al. investigating baseline levels,[19] although numbers are very small.

Gene therapy, emicizumab and inhibition of inhibitors are not associated with peak levels as would be seen with FVIII/FIX prophylaxis. The consequences of not receiving regular peaks on long-term outcomes such as joint status are not well described, although one study suggested a possible protective effect on reducing ABR.[32]

Some people with haemophilia may wish to retain the ability to tailor levels to life style and have access to peak levels at a time of their choosing using standard FVIII/FIX prophylaxis.

6 | CONCLUSIONS

In conclusion, we draw a distinction between studies that report baseline FVIII/FIX data and those that target specific trough levels on prophylaxis and suggest that data cannot be extrapolated from one situation to the other. Prophylaxis should be offered to all people with haemophilia, irrespective of baseline level, if they experience joint or other clinically significant bleeds. Primary prophylaxis should be considered for children with moderate haemophilia, especially those with baseline FVIII/FIX levels between 1 and 3 IU/dl. These recommendations align with recently published UKHCDO guidelines[2] and are the conclusion of other groups.[19] Data are emerging to support higher trough levels for people on prophylaxis, but more studies are required to define the optimum level and this will inevitably vary between individuals. Tailoring to the individual pattern of bleeding remains critically important and often over-rides considerations of trough FVIII/IX levels.[2,12,18,19] High-quality studies to compare long-term outcomes between people treated with FVIII/FIX prophylaxis and non-replacement therapies are required. The current classification of moderate haemophilia covers a very wide phenotype and may need to be reconsidered.

CONFLICTS OF INTEREST

PWC has acted as a paid consultant to Novo Nordisk, Roche and Sobi, received research support from CSL Behring and received support to attend a conference from CSL Behring. SO has received support to attend a conference from Novo Nordisk. HR, DG and RR have no interests to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during for this manuscript.

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