Therapeutic Advances in Hematology Review

Recent advances in musculoskeletal physiotherapy for haemophilia

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Abstract: Physiotherapy is directed towards the movement needs and potential of individuals, providing treatment and rehabilitation to develop, maintain and restore maximum movement and functional ability throughout the lifespan. Recent systematic reviews and randomized controlled trials have extended evidence for the clinical efficacy of physiotherapy interventions and rehabilitation for people with haemophilia. This narrative review synthesizes recent evidence to discuss; differentiating musculoskeletal bleeding and haemophilic arthropathy, efficacy of physiotherapy and rehabilitation for acute musculoskeletal bleeding and arthropathy, as well as monitoring musculoskeletal health. Whilst robust evidence is emerging, there is a need for more well designed randomized clinical studies with larger numbers and homogeneity of participants and collaboration of all researchers and clinicians to identify a core set of outcome measures that can be used to monitor musculoskeletal health.

Keywords: haemophilia, physiotherapy, physical therapy, rehabilitation, bleeding, arthropathy, musculoskeletal

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Introduction

Bleeding into joints and muscles triggering a degenerative process characterized by changes to articular cartilage and other joint structures is the predominant clinical characteristic of haemophilia. End-stage clinical changes include reduced joint range of motion (ROM), flexion contracture, pain and swelling along with imaging indicators of hemosiderin deposits, synovial hypertrophy, cartilage and bone erosion.[1–3] Prevention of arthropathy is therefore the primary goal of haemophilia treatment. Prophylactic therapy with coagulation factor concentrates has been shown to prevent or minimize arthropathy and is standard care for people with the condition.[4,5] Early initiation is ideal, but observational studies demonstrate secondary prophylaxis also has significant success.[5] Emergence of coagulation factor concentrates with extended half life, bypassing agents and gene therapy has potential for people with haemophilia (PWH) to experience a bleed-free life. The challenges for clinicians to deliver optimal musculoskeletal health alongside advances in medical treatment include how to rehabilitate subtle and existing musculoskeletal problems, patients with milder bleeding phenotypes and older patients with progressive arthropathy and increasing frailty.

The World Health Organization defines rehabilitation as 'a set of measures that assist individuals, who experience or are likely to experience disability, to achieve and maintain optimum functioning in interaction with their environments'.[6] Rehabilitation goals include achieving prevention and slowing the rate of functional loss, improving or restoring function, compensation for lost function and maintaining current function. The ability to move is an essential element of health and wellbeing and central to what it means to be healthy.[7] Physiotherapy is directed towards the movement needs and potential of individuals providing rehabilitation and services to develop, maintain and restore maximum movement and functional ability throughout the lifespan.

This review considers recent physiotherapy research relevant to haemophilia musculoskeletal management and the key challenges faced by those responsible for their musculoskeletal care. Well designed randomized controlled trials (RCTs)

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and systematic reviews of these trials provide the highest quality evidence when determining clinical efficacy.[8] Cohort and case-control observational and nonrandomized controlled trials, pre- and poststudy interventional studies, and finally expert opinion follow respectively in the hierarchy of quality evidence. In this review, the Medline, PEDro, Cinahl and The Cochrane Library electronic database were searched from January 2007 to March 2018 using the MeSH terms haemophilia, physiotherapy, haemorrhage, arthropathy, outcome assessment. Systematic reviews of RCTs together with individual RCTs, and where these do not exist, good quality observational and interventional study designs that include comparable homogeneously matched and selected samples, evidence of hypothesis testing and limited bias and influence of confounding variables together with appropriate statistical analysis were selected for review. Six systematic reviews, six narrative reviews, eight RCTs and 32 observational cohort nonrandomized studies are discussed in this review.

How can musculoskeletal bleeding be differentiated from arthropathy and other musculoskeletal disorders?

In countries where prophylaxis is common place, the ankle joint appears the most common site of joint bleeding, whereas, the knee joint is more common when access to prophylaxis is not routine.[9] For individuals receiving prophylaxis, trauma is often the cause of bleeding, whereas in those receiving on-demand treatments, spontaneous and traumatic bleeds are common.[10] Hanley and colleagues[11] described the early signs of bleeding as a sensation of fullness, stiffness, discomfort, pain or tingling at end ROM but with minimal restriction of movement, and often difficult to distinguish from arthritic pain. Moderate bleeding is characterized by increased pain, some swelling and restriction of movement, whilst with severe bleeding, pain is severe, accompanied by marked swelling and almost complete restriction of movement, in other words a 'joint immobilizing bleed'. Accurate diagnosis of a joint bleed in terms of presence or absence is important, as is identifying the site, severity and cause of any joint bleed in order that strategies can be implemented to prevent rebleeding, synovitis, subsequent arthropathy, and guide rehabilitation.

A recent narrative review[12] found limited consensus of symptoms associated with haemarthroses. Symptoms that clinicians associate with haemarthrosis partly overlap with symptoms of haemophilic arthropathy. Interviews with patients and clinicians[13,14] indicate course of symptoms, joint history, type and intensity of pain and impairment in ROM, are used to differentiate bleeding and arthropathy. It is therefore not surprising that half to two-thirds of patient-reported pain or bleeds into joints showed no evidence of haemarthrosis or effusion on ultrasound imaging.[15,16] In painful joints without signs of haemarthrosis, findings of synovitis, tendinitis, enthesitis, bursitis and fat pad inflammation were found. Current research suggests differential diagnosis of bleeding is complex and indicates that clinical consensus on definitions of bleeding are required in order that success of future therapy to treat haemophilia can be monitored. The specialist skills of a physiotherapist or musculoskeletal expert, with good knowledge of joint anatomy as well as an accurate ability to measure and interpret ROM and pain are essential.

Point-of-care ultrasound (POCUS) has potential value in acute haemarthrosis to objectively identify presence of blood in joints, measure size, pinpoint location, assess evolution and confirm complete disappearance.[17] It is not comparable to comprehensive ultrasound examination performed by imaging specialists, but rather a more time-efficient, straightforward, real-time approach to evaluate clinical issues that may affect patient management.[18] Further studies are required to define key ultrasound features of early joint bleeding as well as cessation of bleeding, and whether this can be undertaken at point of care by nonimaging specialist clinicians such as physiotherapists. POCUS is promising but education and training are essential to minimize operator and interpretation variability. Moreover, research is required to model and differentiate pain symptoms of haemarthrosis and haemophilic arthropathy as well as ultrasound features and progression of musculoskeletal bleeding and its resolution. Furthermore, knowledge of paediatric and adult joint features is essential.

Are physiotherapy treatments or rehabilitation interventions effective for restoring function following acute bleeding and preventing rebleeding?

Recent published guidelines on management of haemarthroses recommend early physiotherapy with the aim of symptom control, prevention of

bleed recurrence and joint damage, and restoration of full function and activity.[11,19]

PRICE (Protection, Rest, Ice, Compression, Elevation and rehabilitation) is recommended, although there is limited robust evidence with regards to type and timing of interventions. In sports medicine, a new acronym, POLICE, replacing rest with optimal loading, has been suggested to encourage clinicians to consider the role, type, timing and mechanism of rest and loading of tissue.[20] Optimal loading is an umbrella term for any exercise or therapy intervention and includes traditional interventions like crutches, braces and supports, but also a wide range of manual techniques to restore histological and mechanical properties of soft tissue. Physiotherapy and POLICE management of haemarthroses and supporting evidence is well described in guidelines by Hanley and colleagues.[11] The rationale for protection and rest after acute haemarthrosis is to minimize rebleeding of the fragile synovial tissue.[21] Regarding the load that can be applied, recent animal and *in vitro* studies indicate forced loading of a joint with intra-articular blood results in more cartilage matrix damage when compared with no forced loading.[22,23] Thus, it may be beneficial to avoid weight bearing of a joint with intra-articular blood. However, prolonged rest can negatively affect joint function through reduction in muscle strength, affecting tissue biomechanics and dynamic joint control.[24,25]

No studies have confirmed optimal mechanisms and timing of rest following joint or muscle bleeding, nor timing, optimal and safest method of reloading. Consensus guidelines issued by the World Federation of Haemophilia (WFH) indicate immobilization should commence immediately after a bleed and continue until pain resolves.[10] In practice, a balance should be established between rest, early mobilization and weight bearing to prevent unwanted complications associated with immobilization, while minimizing rebleeding, synovitis and cartilage damage. To combat detrimental effects of rest on muscle function, a programme to restore muscle strength and control is advocated, beginning with isometric contractions, followed by concentric exercises based on a symptom approach. Exercise programmes should be functional and encompass local joint control and global conditioning, as well as weight-bearing activity to improve joint position sense and strength.[11] We found no RCT or controlled observational studies of structured exercise administered in acute and subacute phases following musculoskeletal bleeding, supporting or refuting these expert recommendations. Until further evidence is forthcoming, physiotherapists should be conscious of making a safe transition from rest to full tissue loading after episodes of bleeding within the limits of pain, with full consideration of the injury, severity, nature of damage and abilities of the individual.

A review by Bleakley and colleagues[20] concluded that following soft tissue injury in nonhaemophilia populations there is moderate clinical evidence cold therapy is effective at decreasing short-term pain but has little effect on swelling, recovery time and function. Based on postsurgical and wound healing models rather than closed soft tissue injury, a review paper[26] debated cryotherapy use in managing acute bleeding, concluding it might have potential to increase bleeding by impairing coagulation and haemostasis. In contrast, another review[27] concluded there was no evidence to suggest a negative impact on haemostasis or clinical outcome following acute haemarthrosis in PWH. It is important to acknowledge that attaining temperatures for influencing cellular metabolism of 5–15°C is difficult to achieve in muscles and joints.[20] In a small observational study, d'Young[28] explored the perceived effect of 15 min of cryotherapy in PWH following haemarthrosis. Nine of 12 participants returned questionnaires, with seven reporting reduced swelling, and all nine a positive impact on pain reduction, no increased use of factor concentrate or delayed haemostasis compared with episodes without ice application. Further quantitative evidence from RCTs is required to address this debate. Nevertheless, until evidence is forthcoming, it is probably safe to continue to use cold therapy as part of a pain relief strategy.

The rationale for compression and elevation is to restore pressure gradients within affected tissue. However, there is little evidence to show either has a positive effect on recovery after episodes of bleeding or swelling. Certainly there are no studies in PWH and those within sports medicine are difficult to interpret due to lack of information or large variability in elevation angle time and compression pressure.[20] In recent years, various kinesiology taping techniques have become popular for managing soft tissue oedema. It is hypothesized that application of tape reduces pressure on lymphatic drainage channels, enhancing removal of fluids and other materials that collect in injured

tissue. This seems to contradict the traditional approach of applying an external compressive force to an injury. It is unclear which of the approaches is superior, or whether they can be used interchangeably. We found no published clinical trials evaluating use following haemarthrosis or haematoma, indicating insufficient evidence to support or contradict application of compression, elevation or kinesiology taping following acute joint and muscle bleeding in PWH.

Are physiotherapy treatments or rehabilitation interventions effective in maximizing mobility, function and pain relief in PWH and arthropathy?

Loss of mobility and function in PWH is usually accompanied by chronic pain. Between 35% and 50% of PWH report living with chronic musculoskeletal pain.[29–31] Most recommendations for clinical management of pain, including those from the WFH, relate only to pharmacological management.[10] Effectiveness of physiotherapy rehabilitation for the primary management of pain in osteoarthritis and rheumatoid arthritis is well established.[32] Robust studies evaluating the effects of rehabilitation and physiotherapy for the management of chronic multijoint pain in PWH are required.

Studies have reported between 50% and 80% of PWH avoid exercise and activity due to pain and arthropathy,[33] yet physical activity interventions are encouraged as first-line management for those with other long-term musculoskeletal conditions.[32] Determining effective rehabilitation interventions for PWH has been partly addressed in recent systematic[34,35] and Cochrane reviews.[36] It is not our intention to reproduce these reviews, but it is important to note the reviews highlighted physiotherapy treatment and exercise interventions varied greatly, often involving multiple interventions. Insufficient information along with a diverse range of outcome measures and heterogeneous participants made study comparisons, meta-analysis and establishing clinical efficacy challenging. The systematic review of physiotherapy for chronic arthropathy of the ankle[34] found physiotherapy incorporating some hydrotherapy, strength, balance and proprioception training might lead to significant improvements in ankle ROM and position sense, static and dynamic balance, and pain. A systematic review[35] on the effects of exercise on pain and musculoskeletal function showed supervised and home programmes involving hydrotherapy, resistance exercise or balance training might have the potential to reduce pain, increase ROM and muscle strength. Several studies in the review included manual therapy interventions as well as exercise, therefore the benefits of exercise alone are not clear. A Cochrane review[36] on the effectiveness of exercise showed interventions including at least one of resistance exercises, isometric exercises, bicycle ergometry, treadmill walking and hydrotherapy produced improvement in pain, ROM, strength and walking tolerance. Hydrotherapy may be more effective than land exercises for pain relief; and functional exercises such as treadmill walking and partial weight bearing exercises seem to be more effective than static or short arc exercises for improving muscle strength.

Manual therapy described as the controlled use of manual force applied to articular and soft-tissue structures through mobilization and stretching intended to improve biomechanical elasticity has gained interest as a treatment modality to restore joint function in haemophilic arthropathy. Two studies in PWH[37,38] showed reduction in patient-reported pain but no effect on mobility and function. Two subsequent studies, first a case series observational study ($n = 16$)[39] of joint mobilization to arthropathic knees or ankles of individuals with severe or moderate haemophilia, and second, a small RCT ($n = 16$)[40] investigating the effects of fascial therapy, a form of massage and stretch of soft tissue aiming to releases tightness and restriction on PWH and arthropathy, have been published. Significant improvements in pain and quality of life were reported, but as with previous studies, no improvement in joint health scores and function. Cuesta-Barriuso and colleagues[41] completed a randomized trial of 20 patients and found a combination of a 12-week education and home exercise programme, which included isometric, isotonic and proprioceptive exercises of the ankle, significantly improved the perception of physical health and joint damage.

Parhampour and colleagues[42] compared the effects of a muscle-strengthening progressive resistance training programme and pulsed electromagnetic therapy on joint function in young adult PWH. Forty-eight participants were randomly assigned to one of four groups: resistance training and placebo electromagnetic therapy, resistance training and electromagnetic therapy, electromagnetic therapy only, and no treatment. Statistically significant improvements in joint

function were reported in all groups that included resistance training. In those that received electromagnetic therapy alone, a smaller improvement in joint function was seen in some but not all joints. Improvements in pain were reported for the resistance training group, although data and statistical analysis was not reported. Another RCT of 31 children aged 9–13 years, who had not benefited from routine prophylaxis and demonstrated evidence of early arthropathy, reported high-intensity laser therapy three times per week in addition to standard physiotherapy rehabilitation or exercise showed greater improvements in pain and walking performance in terms of distance walked in 6 min compared with those who received physiotherapy rehabilitation without laser therapy.[43] Although these studies suggest electrotherapy might be beneficial, it is apparent that exercise may enhance the effect.

Since Buzzard and Heim[44] demonstrated a link between AirCast ankle braces and reduced bleeding frequency, splinting, bracing and foot orthosis are used to facilitate joint protection and minimize joint loading. However, no randomized and few controlled trials have investigated efficacy. Small pilot studies have shown neutral-cushioned sports shoes[45] and ankle-foot orthoses[46] may relieve pain for those with ankle arthropathy. Comparing orthopaedic insoles and shoes in PWH and ankle arthropathy, Lobet and colleagues[47] observed comparable improvements in pain, but only the shod condition had an effect on biomechanical walking patterns, notably the propulsive function of the ankle.

Physical activity and aerobic exercise are encouraged and recommended for PWH[48] and efficacy in terms of safety, improvements in strength and mobility have recently been established. In a case-controlled study, Kruger and colleagues[49] compared pain levels pre and post 30 min of treadmill walking at a self-selected speed in 20 adult PWH and aged-matched controls. They found no effect on pain in either group, suggesting this type of exercise is safe for people with chronic haemophilic arthropathy. In a RCT of 64 adults with severe and moderate haemophilia, Runkel and colleagues[50,51] compared a 6-month individualized training programme incorporating mobility, coordination, progressive resistance strength and endurance exercises with a control group. Significant improvements in muscle strength, distance walked in 12 min, single-leg balance time and quality of life domains of general health, mental health, feeling, work, family and endurance were seen in the exercise group, but Gilbert Score joint health was unchanged, apart from a small improvement at the knee joint.

In summary, there is reasonable evidence emerging that exercise *via* its effect on pain, joint ROM, strength and mobility can have a positive impact on maximizing mobility and function as well as quality of life in PWH. However, due to small numbers of studies and diversity of outcomes, it is not possible to conduct a meta-analysis and confirm efficacy. Nevertheless, until evidence is forthcoming, it is reasonable for physiotherapists to continue to use exercise as part of a strategy to relieve pain and improve strength to maximize mobility and function. Programmes incorporating hydrotherapy and functional exercise should be considered. Studies of pulsed electromagnetic, laser and manual therapy show some potential benefit, particularly on pain, but studies are few and low powered, therefore it is not clear whether benefits are due to manual therapy or electrotherapy alone or additional rehabilitation and exercise undertaken. The rationale for splinting, orthoses and footwear to stabilize and alter joint and tissue loading is logical but further evidence is required to demonstrate positive short- and long-term benefits on mobility and function.

How can musculoskeletal health of PWH be monitored?

Until the Haemophilia Joint Health Score (HJHS) was proposed in 2006, evaluation of muscle strength, function or childhood motor development as key outcomes in haemophilia was limited.[52] The HJHS is a validated, systematic and robust measure of joint impairment in children, evaluating structural joint features such as swelling, range of motion, crepitus as well as pain, muscle strength and gait. With increased global use, it appears there is considerable variability among those using the tool, and it might not be sensitive for extremes of good and poor joint health.[53–55] In a retrospective study of 83 boys with severe haemophilia aged 4–18 years, delay in starting prophylaxis, presence of an inhibitor and number of joint bleeds were key factors influencing a positive HJHS score.[53] Recent studies in children and adults comparing POCUS and clinical examination suggest that in 20% of joints, synovial hypertrophy on ultrasound might not be detected by HJHS swelling criteria and degree of joint impairment might be underestimated with

clinical examination.[56–59] With extended half-life factor concentrates, bypassing and gene therapy emerging, it is likely that bleeding episodes and arthropathy will be less evident. It is not known whether simple clinical examinations will be sufficient to monitor musculoskeletal health and there are indications POCUS may complement physical examinations when screening and monitoring joint health of PWH. However, the impact of identifying asymptomatic signs of synovitis on clinical management has yet to be established.

To achieve a comprehensive evaluation and description of health, the World Health Organization adopted the International Classification of Function (ICF) framework[60] suggesting severity of health conditions is best described in terms of 'body structures and functions', 'activities and participation', 'environmental' and 'personal' factors. Activity reflects ability to perform daily tasks while participation reflects involvement in life situations. Current monitoring of haemophilia focuses on joint structure, with little information on function or ability to perform and participate in activities. Several systematic reviews have evaluated measurement properties of tools and measures assessing function, activity and participation.[54,61] Importantly they found none demonstrated adequate measurement properties. For the most part, data on validity, test–retest repeatability and measurement error were lacking, together with limited studies of sufficient size and detail regarding disease severity and treatment. Adult and paediatric versions of the Haemophilia Activities List (HAL, PedHAL) and Functional Independence Score in Haemophilia (FISH) showed adequate construct validity and reliability, along with some discriminative properties.

Increasingly, pressure sensitive mats and dynamic motion capture systems are used to evaluate subtle and complex joint function in health conditions. A retrospective review of gait utilizing the GaitRite identified differences in the way children with haemophilia walked compared with their healthy peers, but more importantly, differences might be related to early joint damage.[62] Subsequent studies using three-dimensional motion capture have identified biomechanical changes in joint health as a result of haemophilic arthropathy despite normal clinical examinations. Key biomechanical markers include longer step time, slower velocity, increased ankle plantar flexion and knee flexion angles and forces during loading in early stance, decreased ankle joint ROM and plantar flexion forces during push off at the end of stance, and reduced hip joint ROM.[63–66] Gait analysis systems are costly and require bespoke expertise and clinical measures of key biomechanical markers of joint health are required.

Links between biomechanical markers, joint arthropathy, physical function and muscle strength are emerging. Alterations in gait patterns of preadolescent boys are associated with negative performance of physical function, and performance depends on their muscle strength.[67] Timed 6 min walk test, timed up and down steps test and knee extensor muscle strength are found to correlate with biomechanical joint function.[67] Groen and colleagues[68] studied a group of boys with haemophilia aged 4–16 years and found lower leg muscle atrophy was weakly associated with self-perceived ability to perform daily activities. Studying adult PWH aged 39 $\pm$ 9 years with arthropathy of the ankle joint, Lobet and colleagues[64] found moderately strong relationships between ankle joint motion, force and power during walking with self-reported pain and stiffness, with no correlation to WFH Orthopaedic and Pettersson radiological score. In adults, lower performance of timed up and go test, which involves standing from a chair, walking 3 m, turning and returning to the chair and sitting down as a measure of lower limb strength and mobility, has been linked with greater arthropathy.[69] This work suggests direct and surrogate measures of muscle strength as well as objective functional performance testing may be important attributes to consider when monitoring musculoskeletal health.

It is becoming well established that self-reported physical activity participation in adult PWH is lower than in people without haemophilia, lower in those with severe disease compared with moderate and mild disease, lower in those not receiving or late starters of prophylaxis, and lower in those with greater arthropathy.[69–72] In paediatric studies, levels of self-reported physical activity of haemophilic children are lower than recommended guidelines for health.[73,74] Nevertheless studies have shown time spent in physical activity are comparable to unaffected peers when prophylaxis is routine. However, self-reported data tend to be overestimated and lack information on intensity and type of activity, so it is not clear from these studies if physical activity is truly

comparable. Furthermore, comparisons of physical activity are challenging due to the influence of socioeconomic status, cultural differences and seasonal effects. All the same, they highlight the need to develop and evaluate interventions that increase physical activity.

Increasingly, wearable activity monitors and mobile health technology are being used to evaluate health outcomes and participation in physical activity. Monitoring physical and sedentary behaviours by tracking real-time body movement with accelerometer and global positioning systems, time of activity as well as type and intensity can be reported. In recent years, studies comparing detailed physical activity parameters using these devices in children and adult PWH with unaffected peers have been published.[75–77] Studies suggest children with severe haemophilia on prophylaxis participate in similar or higher levels of moderate and high-intensity physical activity compared with those with mild haemophilia and unaffected peers. Small sample sizes with large variation in activity levels and lack of age-matched grouping limit interpretation, but as further data emerge and technology advances these provide a promising method of monitoring musculoskeletal health and impact on activity participation.

Integrating a battery of tests evaluating biomechanical function, point-of-care imaging, performance and participation in activities as well as clinical examinations of joint structure has the potential to improve monitoring of musculoskeletal health and subsequent functional modifications. To date, such a battery has not been reported or tested for validity, repeatability responsiveness or sensitivity and until this work is completed there are limitations in recommending this approach and in particular recommending outcome measures that should be used. Just as important are tools that span the generations to enable comparison and prediction of long-term outcomes. Many tests and tools have not undergone validity and reliability testing, which weakens their use as reassessment tools. If monitoring is to occur across different cultures, cross-cultural validity is essential for self-reported questionnaires in which the context question can vary. Furthermore, normative values are often unknown and we do not know which parts of which test are best for predicting and monitoring musculoskeletal health. In addition, regular training, standardized validation and maintenance of competency for those using HJHS, POCUS and other tools are essential. Standardizing a core set of outcomes is necessary whilst minimizing patient burden of multiple assessments.[78]

Conclusion

Recent advances in extending evidence for clinical efficacy of physiotherapy interventions and rehabilitation for PWH through robust systematic reviews and RCTs are applauded. Together with integration of emerging tools and technology such as point-of-care ultrasound, gait and motion analysis, performance-based function tests, physical activity devices and patient-reported activity and participation, this work provides a basis for addressing key challenges faced by clinicians responsible for musculoskeletal care of PWH. Current studies have small sample sizes due to the nature and rarity of haemophilia and this is likely to continue to be a challenge. Therefore, we encourage all researchers and clinicians to identify a core set of outcome measures that will enable future meta-analyses. Evaluation of cost effectiveness is also necessary.[79] Furthermore, we encourage and support the recommendations of Strike and colleagues[36] that there is a need for more well designed randomized clinical studies with larger numbers of participants.

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Conflict of interest statement

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