





ORIGINAL ARTICLE

Needs and challenges among physicians and researchers in thrombosis and hemostasis: Results from an international study

Suzanne Murray BA¹  | Claire McLintock MD²  | Patrice Lazure MSc³ |
 Morgan Peniuta MA³ | Sam Schulman MD, PhD⁴ | Suely M. Rezende MD, PhD⁵ |
 James H. Morrissey PhD⁶   | Thomas Reiser MA⁷ | Ingrid Pabinger MD, PhD⁸

¹AXDEV Group Inc., Brossard, Canada

²National Women's Health, Auckland City Hospital, Auckland, New Zealand

³AXDEV Group Inc., Performance Improvement Research, Brossard, Canada

⁴Department of Internal Medicine, McMaster University, Hamilton, Canada

⁵Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

⁶Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor, Michigan

⁷International Society on Thrombosis and Haemostasis (ISTH), Carrboro, North Carolina

⁸Department of Haematology and Haemostaseology, Medical University of Vienna, Vienna, Austria

Correspondence

Suzanne Murray, 8, Place du Commerce, Suite 210, Brossard, Québec, Canada, J4W 3H2.

Email: murrays@axdevgroup.com

Funding Information

Funding for AXDEV Group to conduct this study came from ISTH education research funds.

Abstract

Background: Specialty societies, such as the International Society on Thrombosis and Haemostasis (ISTH), are a key source of support for clinical and scientific communities, through the provision of educational activities, tools, and resources to support evidence-based care and high-quality, relevant basic science and clinical research.

Objective: The aim of this study was to identify areas where the thrombosis and hemostasis (T&H) community is facing challenges and could benefit from the support of ISTH.

Methods: A 3-phase, mixed-methods study consisting of semistructured individual interviews (phase 1), an online survey (phase 2), and discussion groups (phase 3) was conducted on the challenges experienced by the T&H community. Participants included physicians, clinical and basic science researchers, residents, fellows, students, and industry representatives. Qualitative data were analyzed using thematic analysis. Quantitative data were analyzed using frequency tables and chi-squares.

Results: The study included 468 participants in interviews (n = 45), surveys (n = 404), and discussion groups (n = 19). Nine themes emerged that describe areas where the T&H community may benefit from additional support. Three areas were related to diagnosis and testing: thrombosis risk assessment, genetic testing, and diagnosis of von Willebrand disease (VWD). Another 3 were related to treatment decision making: use of anticoagulants with certain patients, preventive treatments in bleeding disorders, and VWD treatment. The remaining 3 were related to research: collaboration with/among researchers, collaboration between teams to collect data from human subjects, and promotion of basic science research.

Conclusions: This study provides a comprehensive picture of priorities within the T&H community, which should inform the ISTH in its future interventions, including educational offerings and networking opportunities.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2019 The Authors. *Research and Practice in Thrombosis and Haemostasis* published by Wiley Periodicals, Inc on behalf of International Society on Thrombosis and Haemostasis.

KEYWORDS

blood coagulation disorders, clinical competence, hemostasis, medical, research priorities, societies, thrombosis

Essentials

- This was a mixed-methods study in 24 countries to identify areas where ISTH could support the thrombosis and hemostasis community.
- Diagnosis/testing needs identified included thrombosis risk, genetic testing, and von Willebrand disease (VWD).
- Treatment needs identified included anticoagulants, preventive treatments, and VWD.
- Research needs identified included enhanced collaboration and promotion of basic science research.

1 | INTRODUCTION

Hemostatic disorders such as thrombosis and bleeding conditions occur when the process for normal hemostatic equilibrium is altered.¹ Basic science research conducted on coagulation mechanisms has greatly improved scientific knowledge of the complex pathophysiology of coagulation disorders.^{2,3} The past decade has seen significant advancements in technology used to study molecular and pathophysiologic processes in hemostatic disorders.⁴

In the field of thrombosis and hemostasis (T&H), basic science and clinical research has led to considerable advancements in clinical therapies,⁵⁻⁷ including the development of long-acting coagulation factors and gene therapy for patients with hemophilia,⁸ new approaches and agents for anticoagulation to prevent or treat thrombosis,⁹ and new insights into the connection between coagulation, inflammation, and immunity.¹⁰

These advances have led to an increasingly complicated decision-making process, reflected by the complex impact that hemostatic imbalance can have on the complement system, immunity, and inflammation and, therefore, the management of hemostatic disorders.^{11,12} This situation is compounded, in some instances, where access to even basic laboratory testing and medications is limited,¹³ as are opportunities to access the latest scientific knowledge, tests, devices, or medications, compromising provision of optimal clinical care.¹⁴

Given this rapidly evolving context, educational activities are needed to ensure optimal knowledge dissemination to T&H professionals. Specialty societies are in a position to provide support and educational offerings that facilitate access to appropriate resources and tools that enable the production of high-quality, relevant, basic science and clinical research. However, there is currently a lack of research identifying the specific challenges faced by clinicians and researchers — information that is necessary to develop impactful, evidence-based solutions.

Though it is increasingly recognized that educational offerings must be designed on the basis of the learners' needs,^{15,16} often these needs are presumed, rather than objectively determined. To better understand the needs of the T&H community, the International Society on Thrombosis and Haemostasis (ISTH)

conducted a needs assessment of its membership and other professionals in the field. The study objective was to identify areas where the T&H community, including ISTH members, faced challenges and could benefit from the support of a specialty society.

2 | METHODS

The ISTH enlisted AXDEV to carry out a mixed-methods assessment of the needs of the T&H community. Participants were both members and nonmembers, whose professions included physicians, clinical researchers, basic science researchers, residents, fellows, doctoral and postdoctoral students, and industry representatives.

Collection of qualitative and quantitative data was done in 3 consecutive phases. Prior to the first data collection phase, a literature review was conducted to determine the areas of exploration and identify challenges faced by clinicians or researchers. These areas were discussed and refined with subject matter experts to inform the design of the interview guides.

The KSA (knowledge, skills, and attitude) model¹⁷ was used to structure the design of data collection tools. Behavioral and educational researchers in the field of health care (co-authors SM, PL, and MP) executed the study design and data collection, while subject matter experts (co-authors CM, SS, SMR, JHM, TR, and IP) provided scientific and clinical expertise in the field of T&H. Data were interpreted by both groups.

2.1 | Phase 1: Individual interviews

Individuals from 7 different professions and specialties participated in semistructured 45-minute interviews. Interviews consisted of open-ended questions described in Data S1, to prompt discussion and gain an in-depth understanding of participants' perspectives on themes predetermined in the study design phase.¹⁸ Interviews were conducted in English by trained interviewers (including PL, MP, and SM), with questions adapted to the participants' occupation. The most substantive themes that emerged from the qualitative analysis were discussed with subject matter experts and used to inform the phase 2 online survey.

2.2 | Phase 2: Online survey

Survey questions were developed by educational researchers and reviewed by subject matter experts to ensure clinical relevance and validity. The survey aimed to validate the extent to which previously identified challenges or specific perspectives were represented in a larger sample of participants. Response scales and survey sections are described in Data S1. Survey items and examples of questions can be found in Tables 2 and 3. Eligible participants were categorized by their reported profession, and subsequent questions were adjusted accordingly. Surveys were deployed in English only, using vocabulary that is accessible to individuals with another first language. Phase 2 data were then analyzed and triangulated with qualitative data (phase 1) and literature review findings.

2.3 | Phase 3: Discussion groups

Findings from phases 1 and 2 were presented during 90-minute discussion groups at the ISTH 2017 Congress (July 8-13, 2017). These groups included participants from various countries and diverse professions, and aimed to obtain insights as well as potential explanations for the identified challenges. The most substantive themes that emerged from these discussion groups were used in the final triangulation of data, leading to the key findings (see analysis section).

2.4 | Recruitment and inclusion criteria

Potential participants were contacted via the ISTH database. Email invitations were sent to approximately 20 000 professionals (nonmembers and ISTH members from 24 selected countries). Invitations directed potential participants to a secure Web page to complete a screener.

Participants who categorized themselves as clinical physicians or as researchers had to spend at least 50% of their professional time caring for patients or in basic science or clinical research activities, respectively. For the fellow/student/resident category, potential participants had to have reached their fourth year of medical school or to be engaged in doctoral or postdoctoral studies. Industry representatives had to be currently working within the pharmaceutical, biotechnology, or medical devices industry and must have been doing so for at least 2 years. Nurses were excluded, as a separate needs assessment in their profession was being conducted simultaneously.¹⁹ Eligible participants had to be practicing in the targeted countries within each region (see Table 1 legend). Countries were selected to reflect the membership distribution of ISTH and to represent a range of experiences while increasing the comparability of health systems and professional practices. All eligible participants were directed to an informed consent agreement, then either to the survey (phase 2) or to an availability form (phases 1 and 3).

A purposive sampling strategy was used to increase the representativeness of the T&H community by targeting a variety of practice settings (community-based, academic, specialized centers), countries, and years of experience. All subspecialties of clinicians or researchers in the field of T&H were included.

2.5 | Qualitative analysis

Qualitative data obtained from the semistructured interviews (phase 1) and discussion groups (phase 3) were analyzed using a directed qualitative content approach.²⁰ Analysis began with the creation of a coding structure based on preidentified areas of exploration, with more themes added during the coding process. Multiple behavioral and educational researchers coded the transcripts using NVIVO software (QSR International, Cambridge, MA). Interviews were transcribed and coded until the coders unanimously determined that data saturation was reached. Data saturation is defined as a criterion for discontinuing data analysis when no new themes are identified that require creating new categories within the coding structure.^{21,22} The most substantive themes that emerged were organized according to each participant's occupational subgroup.

2.6 | Quantitative analysis

Answers to the online survey (phase 2) were analyzed using SPSS software (version 22.0, IBM Corporation, Armonk, NY) and consisted of frequency tables and cross-tabulations. Participants' answers were dichotomized to identify potential areas of improvement, similar to methods used in previous needs assessments.^{23,24} More detail on this process is provided in Data S1.

Pearson chi-squares with a 0.05 level of significance were used to identify differences between subgroups, based on the participant years of practice/research (ie, ≤ 10 vs. ≥ 11 years) and their main (but not exclusive) domain of practice (ie, thrombosis, bleeding, or both equally).

2.7 | Final analysis and triangulation of data

Triangulation was performed by combining data gathered using qualitative and quantitative methods and from a variety of sources (clinicians, researchers, industry representatives, fellows/residents/students). Convergence and corroboration were sought as a way to minimize biases inherent in using only a single method^{25,26} and to increase the validity and trustworthiness of the findings.²⁷⁻³⁰

2.8 | Ethics

This study received ethics approval from an independent ethics review board (VERITAS, Canada). Individual informed consent was obtained before participation in this study. Participants were entered into a draw for a chance to win registrations to the ISTH 2017 Congress and ISTH memberships.

3 | RESULTS

Of the 1612 members of the T&H community who responded to the study invitations (response rate, 8%), 468 were eligible participants (232 clinicians, 145 basic science or clinical researchers, 59 fellows/residents/students, 32 industry representatives or others).

TABLE 1 Description of sample by region, occupation, and main practice area

| | Asia & Pacific ^b | Eastern Europe ^b | Latin America ^b | Africa & Middle East ^b | North America ^b | Western Europe ^b | Total |
|---|-----------------------------|-----------------------------|----------------------------|-----------------------------------|----------------------------|-----------------------------|------------------------|
| Qualitative sample (phases 1 and 3) detailed by region and occupation – n (% per region) | | | | | | | |
| Clinical physicians | 2 (33%) | 2 (40%) | 6 (43%) | 5 (36%) | 5 (56%) | 4 (44%) | 24 (38%) |
| Researchers (basic science and clinical) | 2 (33%) | 2 (40%) | 7 (50%) | 6 (43%) | 3 (33%) | 3 (44%) | 23 (36%) |
| Students/residents/postdoctoral fellows | 2 (33%) | 1 (20%) | 1 (7%) | 3 (21%) | 1 (11%) | 2 (22%) | 10 (16%) |
| Industry or other ^a | | | | | | | 7 (11%) |
| Total (qualitative) | 6 (9%) | 5 (8%) | 14 (22%) | 14 (22%) | 9 (14%) | 9 (14%) | 64 (100%) |
| Quantitative sample (phase 2) detailed by region and occupation – n (% per region) | | | | | | | |
| Clinical physicians | 31 (66%) | 23 (77%) | 33 (60%) | 26 (60%) | 39 (41%) | 56 (51%) | 208 (51%) |
| Clinical researchers | 2 (4%) | 5 (17%) | 10 (18%) | 3 (7%) | 22 (23%) | 16 (15%) | 58 (14%) |
| Basic science researchers | 12 (26%) | 1 (3%) | 6 (11%) | 7 (16%) | 19 (20%) | 19 (17%) | 64 (16%) |
| Students/residents/postdoctoral fellows | 2 (4%) | 1 (3%) | 6 (11%) | 7 (16%) | 14 (15%) | 19 (17%) | 49 (12%) |
| Industry or other ^a | | | | | | | 25 (6%) |
| Total (quantitative) | 47 (12%) | 30 (7%) | 55 (14%) | 43 (11%) | 94 (23%) | 110 (27%) | 404 (100%) |
| Quantitative sample detailed by region and main practice area for clinicians and clinical researchers – n (% per region) | | | | | | | |
| Thrombosis/clotting | 17 (52%) | 13 (46%) | 20 (47%) | 10 (35%) | 28 (46%) | 38 (53%) | 126 (47%) |
| Hemophilia/bleeding | 6 (18%) | 8 (29%) | 6 (14%) | 9 (31%) | 10 (16%) | 10 (14%) | 49 (18%) |
| Equally in both areas | 10 (30%) | 7 (25%) | 17 (40%) | 10 (35%) | 23 (38%) | 24 (33%) | 91 (34%) |
| Quantitative sample detailed by years of practice/research for clinicians and basic science and clinical researchers – n (% per region) | | | | | | | |
| ≤10 y of practice/research | 18 (40%) | 7 (24%) | 15 (31%) | 20 (56%) | 23 (29%) | 39 (43%) | 122 (37%) |
| 11 y of practice/research or more | 27 (60%) | 22 (76%) | 34 (69%) | 16 (44%) | 57 (71%) | 52 (57%) | 208 (63%) |
| Sample detailed by ISTH membership status – n (% per region) ^c | | | | | | | |
| Member | 39 (72%) | 25 (71%) | 36 (53%) | 31 (54%) | 72 (69%) | 68 (57%) | 287 ^d (62%) |
| Nonmember | 15 (28%) | 10 (29%) | 32 (47%) | 26 (46%) | 32 (31%) | 51 (43%) | 179 ^d (38%) |

^aIncludes laboratory managers and professionals in medical education. As many have worked internationally and have insights into multiple regions, participants were not categorized by region of practice.

^bTargeted countries by region: Asia & Pacific (Australia, China, Japan, New Zealand); Eastern Europe (Poland, Russia); Africa and Middle East (Egypt, Israel, Kenya, Nigeria, Saudi Arabia, South Africa, United Arab Emirates); North America (Canada, United States); Latin America (Argentina, Brazil, Mexico); Western Europe (Austria, France, Germany, Italy, Spain, United Kingdom).

^cTwo participants did not answer.

^dTotals include industry representatives that are not categorized by region of practice.

Individual interviews (phase 1) were conducted with 45 participants, and online surveys (phase 2) were completed by 404 participants. Results from phases 1 and 2 were discussed with 19 participants in 3 live discussion groups (phase 3; Table 1).

Ten key themes that emerged from the triangulated analysis were identified as areas where the T&H community could benefit from additional support (Figure 1) and are detailed in the following sections.

3.1 | Findings related to the diagnosis and testing of coagulation disorders

3.1.1 | Challenges in thrombosis risk assessment

Conducting a clinical risk evaluation in thrombosis emerged as a challenge for participants with a clinical practice. As shown in Table 2,

28% of clinicians reported suboptimal knowledge, given their professional role, of the utilization of risk assessment models for venous thromboembolism (VTE). For subspecialties, 33% of clinicians practicing equally in thrombosis and bleeding disorders reported suboptimal knowledge in this area – this proportion rose to 48% in the subgroup of clinicians practicing mainly (but not exclusively) in bleeding disorders.

When asked specifically about their level of knowledge of the Wells and Geneva scores, 40% of clinicians reported suboptimal knowledge. This proportion rose to 48% for clinicians practicing equally in thrombosis and bleeding disorders. In addition, a total of 36% of clinicians reported suboptimal skills, given their profession, interpreting the Wells and Geneva scores – a proportion that rose to 46% in clinicians practicing equally in thrombosis and bleeding disorders. Skills interpreting the D-dimer test and international

1. Findings related to the diagnosis and testing of coagulation disorders

1.1 Challenges in thrombosis risk assessment

1.2 Challenges with genetic testing in thrombosis and bleeding disorders

1.3 Challenges with diagnosis of von Willebrand disease (VWD)

1.4 Challenges with global assays in T&H field

2. Findings related to treatment decision-making in T&H disorders

2.1 Challenges with anticoagulants in specific patients

2.2 Challenges with preventive treatments in bleeding disorders

2.3 Challenges around treatment of VWD

3. Findings related to research in T&H field

3.1 Challenges around collaboration with and among researchers

3.2 Challenges in collaboration between teams to collect data from human subjects

3.3 Perception that basic research in the field of T&H is not adequately promoted

FIGURE 1 The 10 key themes that emerged from the triangulated analysis: areas where the T&H community could benefit from additional support

normalized ratio results were reported as suboptimal by 22% and 14% of clinicians, respectively (Table 2). A greater proportion of clinicians with less experience reported suboptimal skills interpreting D-dimer tests, compared to those with more experience (31% vs. 17%, $P = 0.007$).

3.1.2 | Challenges with genetic testing in thrombosis and bleeding disorders

The triangulated analysis identified genetic testing as an area where clinicians may benefit from educational interventions. Suboptimal knowledge of when to order genetic testing for thrombosis patients was reported by 31% of clinicians (Table 2), compared to 43% of clinicians when it concerns ordering genetic testing for a patient with a bleeding disorder.

Skills using genetic test results to guide treatment decisions were reported as suboptimal by 33% of clinicians for patients with a thrombotic condition and by 46% with a bleeding disorder (Table 2). A lack of clarity on best practices for genetic testing also emerged as a key theme during the interviews and discussion groups:

I think it affects a whole lot of decisions [the absence of consensus around use of genetic testing] with not just bleeding disorders. But there's no consensus. Guidelines [vary] from country to country, even within countries, even between the institutes in the same country there is not a consensus about guidelines when and why. Workshop participant [#11]

3.1.3 | Challenges with diagnosis of von Willebrand disease

Diagnosing von Willebrand disease (VWD) emerged as a challenging area for clinicians. A total of 35% of clinicians reported suboptimal knowledge of how to diagnose VWD (Table 2). Whereas only a small proportion of clinicians practicing mainly in bleeding disorders reported suboptimal knowledge (6%), more than half (52%) of clinicians who practice mainly in thrombosis disorders and 28% of clinicians practicing equally in both conditions reported suboptimal knowledge ($P < 0.001$).

When asked about their skills in establishing a diagnosis of VWD, 38% of clinicians reported that their skills were suboptimal, with a higher proportion found in clinicians practicing mainly in thrombosis disorders (54%), compared to those practicing mainly in bleeding disorders (12%) or practicing equally in both (32%; $P < 0.001$). The skill gap was higher in less experienced clinicians, compared to those with more experience (Table 2, 47% vs. 33%; $P = 0.024$).

3.1.4 | Challenges with global assays in T&H disorders

Integrating the results of global assays to inform treatment decisions was reported as a challenge. Among all clinicians, 39% reported suboptimal skills using these results to guide treatment (Table 2). In each of the 3 domains of practice, a similar proportion of clinicians reported suboptimal skills in this area.

TABLE 2 Self-reported level of knowledge and skills of clinicians practicing in the field of hemostatic disorders

| Survey questions | Clinician's main (but not exclusive) domain of practice ^a | | | All clinicians | Significant differences by domain ^d | Years of practice ^f | | Significant differences by years of practice ^{e,f} |
|---|--|---------------------------|-------------------------|----------------|--|--------------------------------|--------------|---|
| | Mainly thrombotic disorders | Mainly bleeding disorders | Equally in both domains | | | ≤10 | ≥11 | |
| % (n) of clinicians reported suboptimal knowledge about ^b | | | | | | | | |
| When, why, and how to use risk assessment models for VTE | 16% (22/135) | 48% (25/52) | 33% (35/107) | 28% (82/294) | P < 0.001 | 33% (30/91) | 23% (41/175) | P = 0.10 |
| When, why, and how to apply Wells/Geneva score for DVT risk assessment | 27% (36/134) | 60% (31/52) | 48% (51/107) | 40% (118/293) | P < 0.001 | 41% (37/90) | 37% (64/175) | P = 0.05 |
| When, why, and how to order D-dimer test | 19% (25/134) | 33% (17/52) | 21% (22/107) | 22% (64/293) | P = 0.11 | 24% (22/90) | 19% (34/175) | P = 0.34 |
| When and why to order genetic testing in thrombotic patients | 31% (42/134) | 29% (15/52) | 32% (34/107) | 31% (91/293) | P = 0.93 | 33% (30/90) | 25% (43/175) | P = 0.13 |
| When and why to order genetic testing in bleeding disorders | 59% (80/135) | 19% (10/52) | 33% (35/107) | 43% (125/294) | P < 0.001 | 48% (44/91) | 38% (66/175) | P = 0.10 |
| How to diagnose von Willebrand disease | 52% (70/134) | 6% (3/52) | 28% (30/107) | 35% (103/293) | P < 0.001 | 38% (34/90) | 32% (56/175) | P = 0.35 |
| Type of thromboprophylaxis treatment to use according to patient profile | 19% (25/134) | 40% (21/52) | 34% (36/107) | 28% (82/293) | P = 0.003 | 30% (27/90) | 21% (37/175) | P = 0.11 |
| Use of anticoagulation in patients who have a history of bleeding episodes/bleeding disorders | 25% (34/134) | 40% (21/52) | 41% (44/107) | 34% (99/293) | P = 0.02 | 38% (34/90) | 27% (48/175) | P = 0.08 |
| Timing to reinstate antithrombotic/anti-coagulant medication after hemorrhagic episode(s) | 22% (29/134) | 42% (22/52) | 36% (39/107) | 31% (90/293) | P = 0.01 | 36% (33/91) | 23% (40/174) | P = 0.02 |
| Treatment of bleeding episodes in hemophilia | 72% (96/134) | 8% (4/51) | 41% (43/106) | 49% (143/291) | P < 0.001 | 57% (51/90) | 45% (78/173) | P = 0.08 |
| Long-term treatment to prevent bleeding episodes in hemophilia | 75% (101/134) | 12% (6/52) | 44% (47/107) | 53% (154/293) | P < 0.001 | 62% (56/90) | 47% (82/175) | P = 0.02 |
| Treatment options for von Willebrand disease | 65% (87/134) | 8% (4/52) | 37% (39/106) | 45% (130/292) | P < 0.001 | 52% (47/90) | 38% (66/174) | P = 0.03 |
| % (n) of clinicians reported suboptimal skills about: ^c | | | | | | | | |
| Use and interpretation of Wells/Geneva score for diagnosing DVT | 23% (30/129) | 51% (26/51) | 46% (45/99) | 36% (101/279) | P < 0.001 | 37% (33/90) | 36% (63/173) | P = 0.98 |
| Use and interpretation of D-dimer test | 18% (23/130) | 35% (18/51) | 19% (19/98) | 22% (60/279) | P = 0.03 | 31% (28/90) | 17% (29/173) | P = 0.01 |
| Use and interpretation of international normalized ratio | 12% (15/130) | 26% (13/51) | 11% (11/100) | 14% (39/281) | P = 0.03 | 14% (13/90) | 13% (22/175) | P = 0.67 |
| Use of results from genetic testing to guide treatment of thrombotic disorders | 35% (45/130) | 28% (14/51) | 32% (32/99) | 33% (91/280) | P = 0.65 | 38% (34/90) | 26% (46/174) | P = 0.06 |

(Continues)

TABLE 2 (Continued)

| Survey questions | Clinician's main (but not exclusive) domain of practice ^a | | | All clinicians | Significant differences by domain ^d | Years of practice ^f | | Significant differences by years of practice ^{e,f} |
|--|--|---------------------------|-------------------------|----------------|--|--------------------------------|--------------|---|
| | Mainly thrombosis disorders | Mainly bleeding disorders | Equally in both domains | | | ≤10 | ≥11 | |
| Use of results from genetic testing to guide treatment of bleeding disorders | 61% (79/130) | 18% (9/50) | 41% (41/99) | 46% (129/279) | P < 0.001 | 52% (46/88) | 41% (71/175) | P = 0.07 |
| Diagnose von Willebrand disease | 54% (70/129) | 12% (6/50) | 32% (32/99) | 38% (108/278) | P < 0.001 | 47% (42/89) | 33% (57/173) | P = 0.02 |
| Use of global assay test results to guide treatment | 43% (54/127) | 44% (22/50) | 31% (31/100) | 39% (107/277) | P = 0.14 | 39% (35/90) | 38% (65/171) | P = 0.89 |
| Determine treatment for VTE in cancer patients | 20% (26/130) | 51% (26/51) | 34% (33/98) | 31% (85/279) | P < 0.001 | 32% (28/89) | 27% (47/174) | P = 0.45 |
| Adjust management of anticoagulation in patients who have a severe bleeding episode | 26% (34/130) | 39% (20/51) | 36% (35/97) | 32% (89/278) | P = 0.14 | 36% (32/88) | 28% (48/174) | P = 0.15 |
| Adjust management of anticoagulation in patients who have a nonsevere bleeding episode | 20% (26/130) | 41% (21/51) | 31% (30/97) | 28% (77/278) | P = 0.01 | 32% (28/88) | 24% (42/174) | P = 0.19 |
| Decide type of prophylaxis treatment to use for bleeding episodes | 39% (49/126) | 20% (10/51) | 32% (32/99) | 33% (91/276) | P = 0.05 | 41% (37/90) | 27% (46/171) | P = 0.02 |
| Decide treatment plan for von Willebrand disease | 62% (81/130) | 12% (6/51) | 39% (38/98) | 45% (125/279) | P < 0.001 | 54% (49/90) | 38% (66/174) | P = 0.01 |

DVT, deep vein thrombosis; VTE, venous thromboembolism.

^aQuestion: Which of these broad domains are your professional activities (practice, research, studies) more oriented towards?

^bQuestion: For each statement below, please select the number that best describes your level of knowledge, given your profession. Scale: 1 = Not acceptable given my profession; 3 = Acceptable but could be improved given my profession; 5 = Ideal given my profession.

^cQuestion: For each statement below, please rate your current level of skills in relation to what it should be, given your profession. Scale: 1 = Low; 3 = Acceptable; 5 = Optimal; 6 = Not applicable to my profession. Participants who answered 6 were not included in the frequency tables.

^dPearson chi-squares with a 0.05 level of significance were performed to identify differences between subgroups, according to the 3 domains of practice (ie thrombosis, bleeding, or both domains equally). Significant differences are shown in bold.

^ePearson chi-squares with a 0.05 level of significance were performed to identify differences between subgroups, according to years of practice (≤10 y of practice vs. ≥11 y of practice). Significant differences are shown in bold.

^fStudent and residents having no actual years of practice were excluded from analysis by years of practice.

3.2 | Findings related to treatment decision making in T&H disorders

3.2.1 | Challenges with anticoagulants in specific patients

Challenges related to thromboprophylaxis regimens were also identified. Suboptimal knowledge of the type of thromboprophylaxis regimen to use, according to a patient profile, was reported by 28% of clinicians. In addition, 31% of clinicians reported suboptimal skills, given their role, in determining treatment for VTE in cancer patients (Table 2).

Patients with a thrombotic disorder in addition to a bleeding history also represented a treatment challenge. Suboptimal knowledge of the use of anticoagulant medication in patients with a history of bleeding episodes was reported by 34% of clinicians. This gap was higher among clinicians practicing mainly in bleeding disorders (40%) and those practicing equally in both domains (41%; $P = 0.020$). Specifically, 31% of clinicians reported suboptimal knowledge of the correct timing to reinstate anticoagulants in patients that have had a hemorrhagic episode. A higher proportion of less experienced clinicians reported having a knowledge gap in this area, as compared to more experienced clinicians (36% vs. 23%; $P = 0.022$). Skills in adjusting anticoagulant medication were reported as suboptimal by 32% of clinicians for patients who have had a severe bleeding episode and by 28% for patients who have had a nonsevere bleeding episode (Table 2).

3.2.2 | Challenges with preventive treatments in bleeding disorders

Suboptimal knowledge of treatment for bleeding episodes in people with hemophilia was reported by nearly half of participants (49%). This knowledge gap was self-reported by a majority (72%) of clinicians mainly practicing in thrombosis and by 41% of participants practicing in both areas equally ($P < 0.001$). Suboptimal knowledge of long-term prevention of bleeding episodes in hemophilia patients was also self-reported by clinicians practicing in both domains equally (44%) and clinicians practicing mainly in thrombosis (75%; $P < 0.001$). This proportion was significantly higher among less experienced clinicians, as compared to those with more experience (62% vs. 47%; $P = 0.018$).

One third (33%) of clinicians reported suboptimal skills in deciding the type of prophylaxis treatment to use to prevent bleeding episodes. This proportion rose to 41% among less experienced clinicians, in contrast to 27% of more experienced clinicians ($P = 0.019$).

3.2.3 | Challenges around treatment of VWD

Knowledge of treatment options for VWD was reported as suboptimal by 65% of clinicians practicing mainly in thrombosis and 37% practicing equally in both domains ($P < 0.001$). A significantly higher proportion of less experienced clinicians than those with more

experience also reported suboptimal knowledge of the treatment options for VWD (52% vs. 38%; $P = 0.026$).

A similar situation was found in the self-reported ability to decide on a treatment plan for patients with VWD, as 62% of clinicians practicing mainly in thrombosis and 39% practicing in both domains equally reported suboptimal skills in this area ($P < 0.001$), as did a higher proportion of less experienced than more experienced clinicians (54% vs. 38%, $P = 0.010$). Less experienced clinicians lacking confidence was a recurrent and emerging qualitative theme:

I think von Willebrand disease is hard. It's really hard to make a plan for a patient and if you talk to one doctor and he will tell you, "Oh, I will do this," and then you talk to somebody else and he will say, "I will do that." [...] I don't know if I'm 100% confident about how to approach a von Willebrand patient [...], because I don't think that there's just one answer on that. And I don't have enough years of practicing.

Workshop participant [#25]

3.3 | Findings related to research in the T&H field

3.3.1 | Challenges around collaboration with and among researchers

Collaboration in the research community was among the reported challenges. Over half of researchers (52%) reported that collaborating with other researchers not directly in their area of expertise was difficult (Table 3). Specifically, 39% of researchers perceived that it was difficult to collaborate with clinical researchers. From a list of 12 barriers to conducting research, a "lack of communication between basic science and clinical researchers" was the item most often selected (Figure 2).

A majority of basic science researchers (58%) reported that the creation of networking opportunities for T&H researchers should be given more importance. "Lack of communication between clinicians and clinical researchers" was among the top 3 barriers to optimal care most frequently selected by clinicians (Figure 3). This barrier was more often selected by clinicians practicing mainly in thrombosis (38%) compared to those practicing mainly in bleeding disorders (15%) or equally in both domains (25%).

3.3.2 | Challenges in collaboration between teams to collect data from human subjects

Collecting human data in T&H research was reported as challenging. Nearly half of researchers (46%) reported that data collection from patients was "difficult" or "very difficult" in the context of non-interventional studies; in the context of interventional studies, 41% reported this as difficult.

A specific challenging facet of gathering human data was related to the communication and collaboration needed between physicians and nurses to collect human blood samples:

TABLE 3 Perceptions of T&H researchers

| Survey questions | Researchers whose activities are more oriented toward... | | | All researchers |
|--|--|-------------|--|-----------------|
| | Thrombosis | Bleeding | Both domains | |
| % (n) of researchers that perceived the following as difficult or very difficult ^a | | | | |
| Collaborating with other researchers <i>not</i> directly in my area of expertise | 47% (29/62) | 55% (11/20) | 57% (30/53) | 52% (70/135) |
| Collaborating with clinical researchers | 32% (20/63) | 43% (9/21) | 45% (26/58) | 39% (55/142) |
| Collecting data from patients in the context of noninterventional studies | 36% (20/55) | 68% (13/19) | 49% (22/45) | 46% (55/119) |
| Collecting data from patients in the context of interventional studies | 35% (18/52) | 43% (6/14) | 49% (17/35) | 41%(41/101) |
| General facets of research | % (n) selected that should have <i>more</i> importance | | % (n) selected that should have <i>less</i> importance | |
| % (n) of researchers that selected these aspects as ones that should be given <i>more</i> importance in the T&H field ^b | | | | |
| Creation of networking opportunities for researchers | 58% (62/107) | | 5% (5/107) | |
| Promoting and stimulating T&H basic science research | 67% (72/108) | | 6% (6/108) | |
| Support for large multisite, multicountry studies | 49% (52/107) | | 16% (17/107) | |
| Research topics | % (n) selected "should have <i>more</i> importance" | | % (n) selected "should have <i>less</i> importance" | |
| % (n) of researchers that selected these topics as ones that should be given <i>more</i> importance in the T&H field ^b | | | | |
| Link to and relation between immune response, inflammation, and coagulation | 69% (74/108) | | 4% (4/108) | |
| Link between cancer and thrombosis | 63% (69/109) | | 5% (5/109) | |
| Support the development of personalized medicine in the thrombosis and hemostasis field | 61% (66/108) | | 7% (7/108) | |
| Contributions of the clotting and fibrinolytic systems to nonhemostatic processes in general | 50% (53/107) | | 9% (10/107) | |
| Role of platelet physiology in nonhemostatic systems | 46% (50/109) | | 13% (14/109) | |
| Development of animal models for basic science research | 42% (45/108) | | 19% (21/108) | |
| Novel causes (including genetic) of bleeding disorders | 41% (44/108) | | 12% (13/108) | |
| Role of the coagulation system in arterial thrombosis | 36% (39/108) | | 7% (7/108) | |
| Engineering of less immunogenic factor concentrates | 27% (29/106) | | 23% (24/106) | |
| Relation between neutrophil extracellular trap, the contact pathway, and thrombosis | 25% (26/108) | | 10% (11/108) | |
| Role of platelet polyphosphates in hemostasis and thrombosis | 23% (25/108) | | 18% (19/108) | |
| Immunological basis of hemophilia inhibitors | 23% (24/104) | | 17% (18/104) | |
| Immunological basis of immune thrombocytopenia | 12% (13/105) | | 24% (25/105) | |

T&H, thrombosis and hemostasis.

^aQuestion: Please rate your current level of difficulty in relation to these research tasks. Scale: 1 = Very difficult; 4 = Very easy; 5 = Not relevant to me. Participants who selected 5 were not included in the table.

^bTo the best of your knowledge, do you think these research aspects or topics should be given: 1. More importance; 2. The same importance; or 3. Less importance by the research community in the field of thrombosis and hemostasis?

The main problem with such studies is that doctors just get to collect blood for the point of the study, and the biggest challenge is to make them collect blood in time, in those points that we study.

Clinical researcher, Russia [#43]

support of multisite and multicountry studies should be given more importance, according to 49% of researchers.

When asked which topics should be better promoted among the research community in T&H, researchers cited 2 topics: the relationship between immune response, inflammation, and coagulation (69%); and the link between cancer and thrombosis (63%) (see Table 3 for details).

3.3.3 | Perception that basic science research in the field of T&H is not adequately promoted

A majority of researchers (67%) indicated that promoting and stimulating basic science research should be given more importance by the research community in the field of T&H. Specifically, better

4 | DISCUSSION

This mixed-methods study aimed to identify areas where the T&H community faced challenges and therefore could benefit from the support of a specialty society. Three broad challenge areas emerged:



FIGURE 2 Barriers to conducting research in T&H field

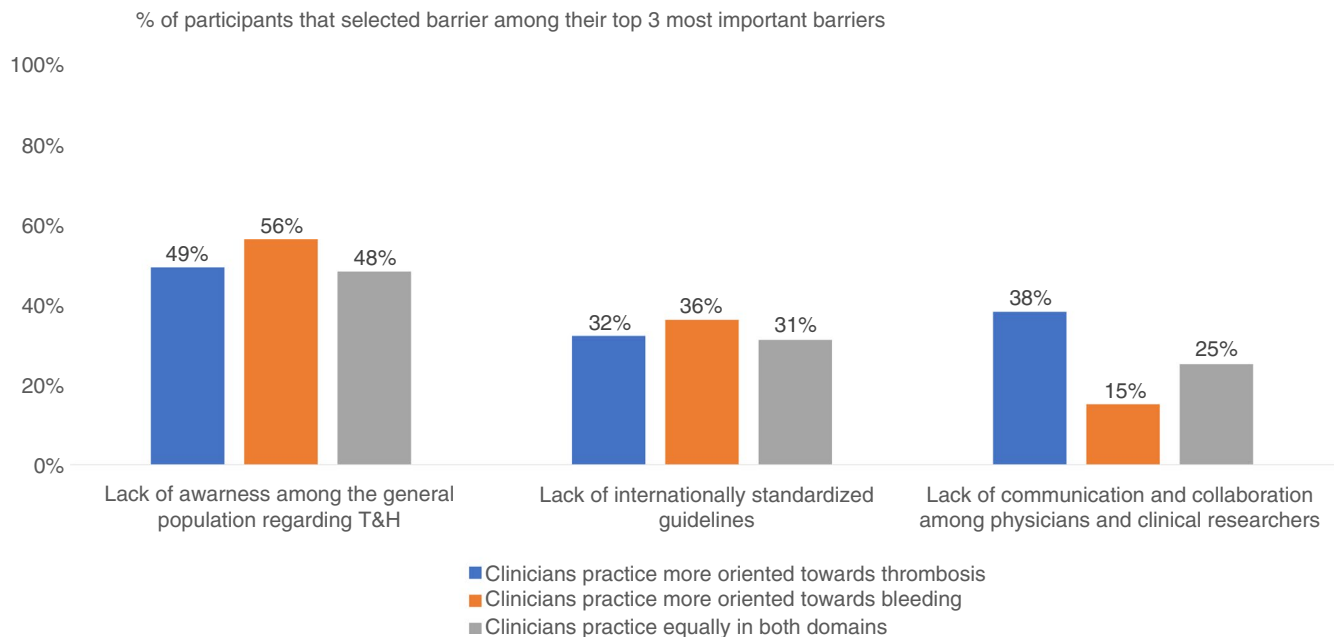


FIGURE 3 Barriers to providing optimal care

diagnosis and testing of coagulation disorders, treatment decision making, and researcher-specific challenges. Study results indicated that within these core areas, clinicians had a suboptimal level of skills and knowledge of issues outside their specialty area; clinicians with less experience reported greater challenges; and collaboration between stakeholders in T&H was challenging across subspecialties and professional roles.

This study provides a platform to discuss the consequences of these core challenges on health care systems and to consider the contextual factors that may have affected the findings. The present discussion articulates the potential root causes and

implications of these findings. Some of the study findings underscore the need for further educational offerings on topics that are consistent with the required competencies of clinicians practicing in T&H, as reported in the clinical core curriculum developed by the ISTH.³¹

Participants who work primarily in bleeding disorders reported challenges when conducting risk assessments for VTE and when deciding when to order (and how to interpret) genetic tests. Conversely, those who specialize in thrombosis experienced challenges diagnosing and planning treatments for patients with VWD. Participants in either specialization generally reported greater skill

and knowledge levels when operating within their main area of practice, compared to those who practice in both areas, which is not unexpected. Making decisions regarding the treatment and prevention of bleeding episodes in hemophilia patients was challenging for nearly half of those working equally in T&H, and in an even greater proportion of those who mainly (but not exclusively) work in the field of thrombosis.

The gaps in knowledge of certain issues related to T&H are concerning. For instance, when a thrombosis risk assessment is not performed properly, VTE diagnosis can be missed, and diagnostic imaging is likely to be overused. A lack of knowledge of how to perform a risk assessment, or which thromboprophylaxis method to use according to a patient's profile, may place patients at risk for VTE or a bleeding episode if thromboprophylaxis is inappropriately prescribed. The observed gaps relating to the diagnosis and treatment of VWD suggest how underreporting, and a lack of skills to treat the disease could put the patient at risk of bleeding. The reporting of suboptimal skills using results of global assays to guide treatment may, however, in part reflect participants' perception that these assays lack definition in current clinical management of bleeding and clotting disorders due to their inherent limitations rather than the individual's lack of knowledge. Nevertheless, since these assays are increasingly used,³² education is required to clarify their role and define their limitations.

This study found that clinicians with <10 years of experience reported challenges in interpreting test results, both for diagnosis purposes and when making treatment decisions for bleeding disorders, especially VWD. As was anticipated, clinicians with more practice in the field of thrombosis had less confidence in diagnosis and treatment of patients with hemorrhagic disorders and vice versa. These variables could help inform the design of educational and professional development programs.

Researchers described how communication and collaboration posed a challenge, whether with researchers in- or outside their subarea of expertise, with clinicians, or in collaborations with industry. These difficulties are perceived as primary barriers to research and may hinder the potential benefits of collaboration. This finding parallels a recent needs assessment of knowledge and skills among clinical researchers in thrombosis, who reported gaps in their skills related to teamwork, time management, and leadership, in addition to confidence gaps pertaining to knowledge translation and grant writing and review.³³ Interestingly, these gaps were not observed in our study. This difference could be explained by the fact that this Canadian study was conducted with research faculty only, whereas our study involved a broader research community.

Researchers also indicated that there is a need for the ISTH and the T&H community to better externally promote and support basic science research and to increase awareness of the crucial role basic science research plays in driving new treatments and clinical practices.³⁴

4.1 | Study limitations

Although this study identified key gaps in knowledge, skills, and attitude in T&H, future studies explaining the exact root causes of

these gaps are warranted, especially at a local level. Data collected were based on self-reports rather than objective observational data. The sample size was appropriate for this type of exploratory mixed-methods study; however, given that the total sample size was distributed across several regions and divided between clinicians and researchers, subgroup findings should be interpreted as indicators only. Perception of patients were not included in this initiative.

There is a risk of selection bias regarding both the participants in the different study phases and the initial choice of general areas to be presented in the interviews.

This study included but did not distinguish between participants from developed and developing countries, which poses limitations on how the findings should be generalized. In all instances, responses likely varied depending on the participants' access to research facilities or funding, their individual professional role, and the presence or absence of collaboration opportunities or an expert consensus on best practices.

Illustrative quotes from workshop participants were reported, but the exact profession and country of practice were not due to difficulties distinguishing the identity of a speaker from a recorded group discussion.

4.2 | Conclusions

Educational interventions should be designed to broaden the knowledge and skills of clinicians across the entire field of T&H, with emphasis on those practicing equally in both domains, as a way to provide consistent patient care. These educational offerings should focus on the 7 key themes that emerged from the triangulated analysis as areas of priorities around the diagnosis and testing of coagulation disorders and in relation to treatment decision making in T&H disorders. Findings related to research in T&H demonstrate a need for enhanced networking and collaboration opportunities, as well as increased promotion of basic science research.

ACKNOWLEDGMENTS

This study was conducted by AXDEV Group. The authors acknowledge the support of project manager Olivier Jacob and project coordinator Marc Distexhe, who supported the research team and steering committee by facilitating data collection and analysis and by coordinating communication between the many contributors to this project. Sara Labbé (researcher, AXDEV Group) and Sophie Péloquin (director of performance and strategy, AXDEV Group) contributed to data collection and analysis, the design and presentation of the final findings, and the development of this manuscript. The authors also thank Christine Candora-Hickey (ISTH), without whom this study would not have been possible. Finally, the authors sincerely thank each physician, researcher, and stakeholder for their valuable participation in this study.

RELATIONSHIP DISCLOSURE

SM is the CEO and Founder of AXDEV Group Inc. PL and MP are employees of AXDEV Group Inc. JHM reports equity ownership from

PrevThro Pharmaceuticals, consulting from Cayuga Pharmaceuticals, research support from Kerafast, Inc., and grants from National Institutes of Health. TM is an employee of the International Society on Thrombosis and Haemostasis (ISTH). CM, SS, SMR and IP have nothing to disclose in relation to the published work.

AUTHOR CONTRIBUTIONS

SM oversaw the overall study design and applied her expertise to the interpretation of findings and critical decision making on the content of this manuscript. PL led the study design and development of research tools, as well as the quantitative and qualitative analysis and the interpretation of findings. In addition, he supervised development of the manuscript first draft and integration of co-authors' comments. MP participated in the development of research tools, data collection, data analysis, and the interpretation of findings and was instrumental in the development of the manuscript. TR was involved in the study design and applied his expertise to the interpretation of findings and development of the manuscript. CM, SS, SMR, JHM, and IP were part of the steering committee and contributed their expertise in thrombosis and hemostasis to this project by collaborating on research design and the interpretation of findings. The steering committee offered guidance and contextualization of data to support the creation of this manuscript. Each co-author has contributed sufficiently to be considered an author of this article, according to the International Committee of Medical Journal Editors' requirements, and each co-author critically reviewed the draft and approved the final version submitted.

ORCID

Claire McLintock  <https://orcid.org/0000-0002-4771-8760>

James H. Morrissey  <https://orcid.org/0000-0002-1570-1569>

REFERENCES

- Fredenburgh JC, Weitz JI. Overview of hemostasis and thrombosis. In: Hoffman R, Benz J, Edward J, Silberstein LE, Heslop HE, Weitz JI, et al., editor. *Hematology: Basic Principles and Practice*. 7th ed. Philadelphia, PA: Elsevier; 2018:1831–42.
- Agarwal A, Depa N, Singh G, Chawla K. Exploring the field of hematology and thromboembolism with Dr. Jeffrey Weitz. *Univ Toronto Med J*. 2016;93:39.
- Gonzalez Guerrero C, Montoro Ronsano JB. Physiopathology and treatment of critical bleeding: a literature review. *Farm Hosp*. 2015;39:382–90.
- Weitz JI, Eikelboom JW. Advances in thrombosis and hemostasis: an introduction to the compendium. *Circ Res*. 2016;118:1337–9.
- Gómez-Outes A, García-Fuentes M, Suárez-Gea ML. Discovery methods of coagulation-inhibiting drugs. *Expert Opin Drug Discov*. 2017;12:1195–205.
- Sehgal A, Barros S, Ivanciu L, Cooley B, Qin J, Racie T, et al. An RNAi therapeutic targeting antithrombin to rebalance the coagulation system and promote hemostasis in hemophilia. *Nat Med*. 2015;21:492–7.
- Tuddenham EG. Platelets are a safe way to deliver factor VIII. After 13 years of preclinical research it is now time for a clinical trial. *J Thromb Haemost*. 2017;15:96–7.
- Swystun LL, Lillicrap D. Gene therapy for coagulation disorders. *Circ Res*. 2016;118:1443–52.
- Weitz JI, Fredenburgh JC. Factors XI and XII as targets for new anticoagulants. *Front Med*. 2017;4:19.
- Long AT, Kenne E, Jung R, Fuchs TA, Renne T. Contact system revisited: an interface between inflammation, coagulation, and innate immunity. *J Thromb Haemost*. 2016;14:427–37.
- Gulati D, Novak A, Stanworth SJ. Common haemostasis issues in major bleeding and critical illness. *Clin Med*. 2018;18:320–3.
- Leebeek FWG, Susen S. Von Willebrand disease: clinical conundrums. *Haemophilia*. 2018;24(Suppl 6):37–43.
- Etulain J. Unique challenges and experiences of trainees from Reach-the-World countries. *J Thromb Haemost*. 2016;14:1495–7.
- Stoffman J, Andersson NG, Branchford B, Batt K, D'Oiron R, Escuriola Ettingshausen C, et al. Common themes and challenges in hemophilia care: a multinational perspective. *Hematology*. 2018;1–10.
- Robertson MK, Umble KE, Cervero RM. Impact studies in continuing education for health professions: update. *J Contin Educ Health Prof*. 2003;23:146–56.
- Cervero RM, Gaines JK. Effectiveness of continuing medical education: updated synthesis of systematic reviews. Chicago, IL: Accreditation Council for Continuing Medical Education; 2014.
- Sandelowski M. Using qualitative research. *Qual Health Res*. 2004;14:1366–86.
- Dicicco-Bloom B, Crabtree BF. The qualitative research interview. *Med Educ*. 2006;40:314–21.
- Lazure P, Munn J, Labbé S, Murray S, Butler R, Khair K, et al. Education needs of nurses in thrombosis and haemostasis: an international, mixed-methods study. *Res Pract Thromb Haemost*. 3:99–108.
- Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Rephils*. 2005;15:1277–88.
- Kerr C, Nixon A, Wild D. Assessing and demonstrating data saturation in qualitative inquiry supporting patient-reported outcomes research. *Expert Rev Pharmacoecon Outcomes Res*. 2010;10:269–81.
- Glaser BG, Strauss AL. *The discovery of grounded theory: strategies for qualitative research*. Chicago: Aldine; 1967.
- Murray S, Labbe S, Kothare S, Malaga I, Kluger G, Ogden P, et al. Identifying the educational needs of physicians in pediatric epilepsy in order to improve care: results from a needs assessment in Germany, Spain, and the United States. *Epileptic Disord*. 2018;20:239–56.
- Murray S, Carrera C, Lazure P, Vardas P, Zamorano JL, Kearney P, et al. Identifying the needs for competency-based education in Europe: a needs assessment of cardiologists across 52 countries. *J Eur CME*. 2017;6:1337478.
- Denzin NK. *The research act: a theoretical introduction to sociological methods*. Englewood Cliffs, NJ: Prentice Hall; 1988.
- Greene JC, Caracelli VJ, Graham WF. Toward a conceptual framework for mixed-method evaluation designs. *Educ Eval Policy Anal*. 1989;11:225–74.
- Bogdan R, Biklen S. *Qualitative research in education: an introduction to theory and methods*. Boston, MA: Allyn & Bacon; 2006.
- Patton MQ. Enhancing the quality and credibility of qualitative analysis. *Health Serv Res*. 1999;34:1189–208.
- Johnstone PL. Mixed methods, mixed methodology health services research in practice. *Qual Health Res*. 2004;14:259–71.
- Maudsley G. Mixing it but not mixed-up: mixed methods research in medical education (a critical narrative review). *Med Teach*. 2011;33:e92–104.
- McLintock C, Pabinger I, Bauer KA, Laffan M, Angchaisuksiri P, Rezende SM, et al. International Society on Thrombosis and

- Haemostasis core curriculum project: core competencies in clinical thrombosis and hemostasis. *J Thromb Haemost.* 2016;14:3–27.
32. Brummel-Ziedins KE, Wolberg AS. Global assays of hemostasis. *Curr Opin Hematol.* 2014;21:395–403.
 33. Skeith L, Carrier M, Shivakumar S, Langlois N, Le Gal G, Harris I, et al. Guiding curriculum development of a national research training program in thrombosis medicine: a needs assessment involving faculty and trainees. *Thromb Res.* 2018;162:79–86.
 34. Begley CG, Ioannidis JPA. Reproducibility in science: improving the standard for basic and preclinical research. *Circ Res.* 2015;116:116–26.

How to cite this article: Murray S, McLintock C, Lazure P, et al. Needs and challenges among physicians and researchers in thrombosis and hemostasis: Results from an international study. *Res Pract Thromb Haemost.* 2019;3:626–638. <https://doi.org/10.1002/rth2.12237>

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.