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SHORT COMMUNICATION

An update on quality control for the PFA-100/PFA-200

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Abstract

Testing of platelet function comprises a crucial element of hemostasis assessment, particularly for investigations into bleeding and/or bruising. The Platelet Function Analyzer (PFA)-100 is the most utilized primary hemostasis-screening test system available, as recently remodeled/upgraded to the PFA-200. Internal quality control (IQC) and external quality assessment (EQA) (including proficiency testing) represent critical elements of ensuring test practice quality. Although true for all tests, IQC and EQA are logistically challenging for platelet function testing, inclusive of the PFA-100/200. We accordingly update our experience with novel yet feasible approaches to both IQC and EQA of PFA-100/200. Over the past 10 years, a total of 43 challenges have been tested, with most challenges designed to mimic moderate or severe primary hemostasis defects. The current report is restricted to the last four years and has also differentially assessed PFA-100 vs. PFA-200 EQA results to identify potential variance. Numerical results for closure times (CTs) and participant-supplied interpretive comments were analyzed. Reported CTs for each challenge were within limits of expectation, and good reproducibility was evidenced by repeated challenges. Coefficients of variation (CVs) for challenges, generally ranging from 15% to 25%, were similar or better than those obtained using native whole blood and consistent with past reports. Participant interpretations were generally consistent with test data and expectations. There was no evident difference in PFA-100 vs. PFA-200 EQA test results. The EQA material has also been successfully evaluated from the perspective of potential IQC. To conclude, IQC and EQA processes for the PFA-100/200 have been established that are highly reproducible, supporting the concept of EQA/IQC for platelet function testing, and also facilitating monitoring and improvement in its performance. In terms of EQA, PFA-100 and PFA-200 instruments appear to behave similarly.

Keywords

EQA, external quality assessment, internal quality control, IQC, Platelet Function Analyzer, PFA-100, PFA-200, proficiency testing

History

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Introduction

Testing of platelet function comprises a crucial element of comprehensive hemostasis assessment for investigations into bleeding and/or bruising and also can be implemented to assess antiplatelet therapy (1–4). Classically, testing of platelet function is complex, specialized, time-consuming, and performed using either light transmittance aggregometry (LTA) or whole blood aggregometry (WBA) (1–4). Given test complexity and time requirements, alternate (simpler) methodologies may be used to assess (and potentially monitor) various antiplatelet therapies, or screen for primary hemostasis disorders (e.g., von Willebrand disease (VWD) and platelet function defects) (4,5). For platelet function 'screening,' the Platelet Function Analyzer (PFA)-100 (Siemens Healthcare, Marburg, Germany) is the system most globally utilized, as recently remodeled/upgraded to the PFA-200 (5). However, the PFA-200 is not universally available worldwide (e.g., not yet available in the US), the vast user experience is with the PFA-100, and it is unclear how comparable the models are in terms of performance.

External quality assessment (EQA), sometimes alternatively or additionally referred to as 'proficiency testing' and internal quality control (IQC) are central procedures for assuring the quality of laboratory testing, as characteristically also applied to most hemostasis tests (6,7). However, EQA and IQC for platelet function tests are particularly challenging, for reasons extensively reviewed elsewhere, but largely centering on the inability to generate stable EQA and IQC materials containing a platelet milieu (1,8). Although some variability in practice has been reported for the PFA-100 (mostly related to test usage and normal reference ranges) (9), classical platelet aggregometry-based platelet function testing is arguably even less well standardized (1,10,11). Such inconsistencies potentially compromise the clinical value of testing. Thus, novel approaches to EQA and IQC for testing of platelet function have potential value in standardizing and improving test practice. We therefore wish to report and update our experience, last reported in 2014 (12), regarding a successful EQA process as so far applied to PFA-100/200 testing for the past 10 years. This is potentially also adaptable to IQC practice, and also other test systems for assessing platelet function. The current report evaluates EQA data for the past four years (2014–2017 inclusive) and also PFA-100 vs. PFA-200

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Table I. Summary of wet challenges undertaken by laboratories as per updated current report (2014–2017).

Year and wet challenge sample identity[a]	Scenario that sample designed to mimic	Target PFA-100/200 CTs[b]		Median (95% CI) CTs		CVs (%)	
		C/ADP (s)	C/Epi (s)	C/ADP (s)	C/Epi (s)	C/ADP	C/Epi
2014 – Dispatch 1 baseline	Normal baseline CTs	Normal	Normal	84 (78–87)	116 (108–119)	15.9	16.1
2014 PF14-03[a]	Normal (no additive tube)	Normal	Normal	95 (85–106)	123 (114–133)	20.0	22.6
2014 PF14-03b	Severe defect	>250	>250	301 (301–301)	301 (301–301)	17.1	14.9
2014 – Dispatch 2 baseline	Normal baseline CTs	Normal	Normal	83 (80–88)	130 (116–136)	15.1	15.3
2014 PF14-08a	Severe defect	>250	>250	301 (283–301)	301 (301–301)	19.1	10.2
2014 PF14-08b	Moderate/severe defect	>200	>200	301 (301–301)	301 (301–301)	9.8	10.1
2015 – Dispatch 1 baseline	Normal baseline CTs	Normal	Normal	88 (79–94)	119 (112–125)	17.5	18.0
2015 PF15-03a	Moderate/severe defect	>200	>200	301 (301–301)	301 (301–301)	16.9	5.4
2015 PF15-03[b]	Normal (no additive tube)	Normal	Normal	98 (90–106)	132 (112–125)	26.2	29.8
2015 – Dispatch 2 baseline	Normal baseline CTs	Normal	Normal	87 (81–92)	117 (113–123)	16.6	15.5
2015 PF15-08[a]	Severe defect	>250	>250	301 (301–301)	301 (301–301)	16.2	13.2
2015 PF15-08[b]	Normal (no additive tube)	Normal	Normal	97 (91–107)	127 (119–144)	22.1	24.3
2016 – Dispatch 1 baseline	Normal baseline CTs	Normal	Normal	83 (79–86)	116 (110–124)	12.6	15.7
2016 PF16-03[a]	Severe defect	>250	>250	301 (301–301)	301 (301–301)	9.1	12.8
2016 PF16-03[b]	Normal (no additive tube)	Normal	Normal	94 (89–103)	122 (118–133)	18.8	25.2
2016 – Dispatch 2 baseline	Normal baseline CTs	Normal	Normal	86 (81–92)	112.5 (106–118)	17.9	21.6
2016 PF16-08[a]	Normal (no additive tube)	Normal	Normal	97 (94–105)	129 (122–134)	22.1	24.5
2016 PF16-08[b]	Moderate/severe defect	>200	>200	301 (262–301)	301 (301–301)	23.0	13.1
2017 – Dispatch 1 baseline	Normal baseline CTs	Normal	Normal	84 (80–90)	116.5 (110–126)	16.7	17.0
2017 PF17-03a	Moderate/severe defect	>200	>200	301 (301–301)	301 (301–301)	15.7	11.8
2017 PF17-03b	Normal (no additive tube)	Normal	Normal	95 (80–90)	125 (120–133)	19.2	29.1
2017 – Dispatch 2 baseline	Normal baseline CTs	Normal	Normal	85 (82–88)	118 (110–125)	15.2	16.7
2017 PF17-08a	Normal (no additive tube)	Normal	Normal	97 (89–103)	125 (119–129)	18.9	18.2
2017 PF17-08b	Severe defect	>250	>250	301 (301–301)	301 (301–301)	15.6	13.3

[a]Four (2 × 2) samples are dispatched to participants per year with expected performance in March and August. Some similarly or identically formulated challenge samples are dispatched in different exercises to help assess reproducibility of the system. 'Baseline' data represents data within each exercise using native whole blood prior to test challenges.

[b]'Normal' means CTs within the normal reference range. All challenges were essentially deemed to be successful. Similar sample sets are identified by scenario (e.g., all challenges that represent no additive, or all challenges that mimic severe defect). Identical sample sets are those that comprise the same challenge material sent in different surveys; viz: PF14-03b and PF14-08a; PF14-08b and PF15-03a; PF15-08a and PF16-03a; PF17-08b and PF17-03a.

CTs: closure times; CVs: coefficients of variation; C/ADP: collagen/adenosine diphosphate; C/Epi: collagen/epinephrine; PFA-100/200: Platelet Function Analyzer-100/200; CI: confidence interval.

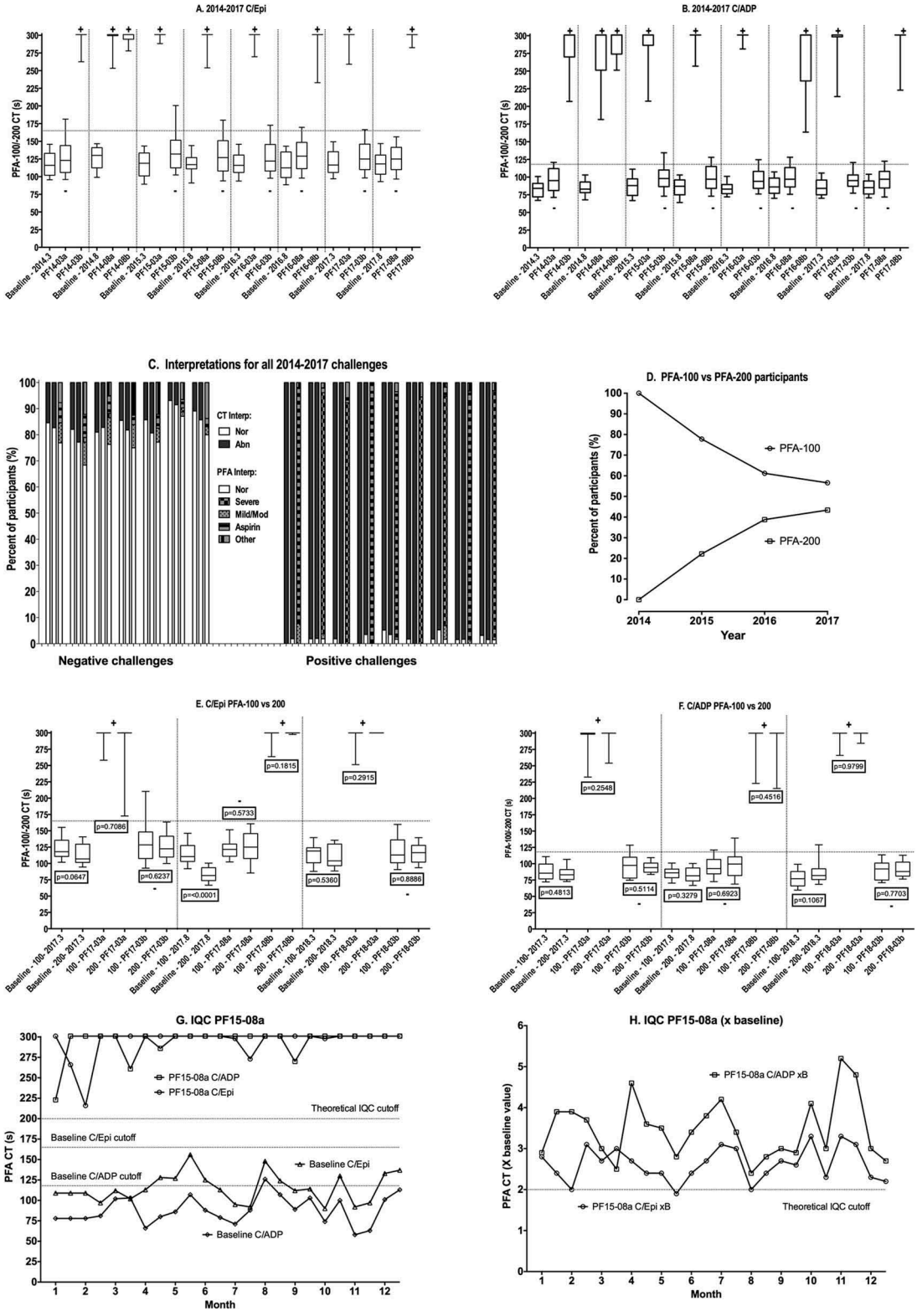

Figure 1. (A and B) PFA-100/200 closure time (CT) data (seconds, y-axes) reported by participants of the RCPAQAP Haematology external quality assessment (EQA) module as described in this report, and shown as box plots (showing median and 10th/90th percentiles), and specifically for 2014–2017 inclusive, and C/Epi and C/ADP, respectively. Horizontal dashed lines in each figure indicate upper limit of normal reference range for C/ADP or C/Epi cartridges (as appropriate) according to product information booklet. Note that individual laboratory normal ranges may differ and thus interpretation of CT data (as normal or prolonged) would also vary accordingly. Note: '+' = 'positive' challenge; '−' = 'negative' challenge (= non-additive tubes), as compared to baseline CT values. Individual challenges are identified on the x-axis as per Table I. (C) Participant interpretations related to CTs obtained using challenge tubes identified in Figure 1A and 1B (i.e., as either 'normal' [= within their normal CT reference range for that test cartridge] or 'abnormal' [= above their CT reference range]; first bar in each set = C/Epi; second bar in each set = C/ADP), as well as overall PFA test interpretations related to the pattern of test results obtained (third bar in each set, as 'normal', 'severe primary hemostatic defect', 'aspirin-like' results, 'mild/moderate' primary hemostatic defect (see also Table I). 'Other' indicates an alternate interpretation provided by participant. Individual challenges are identified in Table I and are in order: Negative challenges: PF14-03a, PF15-03b, PF15-08b, PF16-03b, PF16-08a, PF17-03b, PF17-08a; Positive challenges: PF14-03b, PF14-08a, PF14-08b, PF15-03a, PF15-08a, PF16-03a, PF16-08b, PF17-03a, PF17-08b. (D): The changing face of the PFA. Percent of EQA participant laboratories reporting to use the PFA-100 vs. the PFA-200 from 2014 to 2017 inclusive. (E and F) Comparative data

comparatively for the most recent data sets available to assess potential differences.

Materials and methods

PFA-100/200 instrument overviews

The history and background to the PFA-100/200 has been previously extensively reviewed (5,13). In brief, both PFA-100 and PFA-200 systems employ similar mechanical processes, but the PFA-200 has more advanced software and a modern user interface including a touch screen. Both employ the same test cartridge system, with three cartridge types potentially available depending on geography. One has a collagen (2 μg equine type I) and epinephrine (10 μg)-coated membrane (C/Epi); another has a collagen (2 μg equine type I) and adenosine-diphosphate (50 μg)-coated membrane (C/ADP); and a third has a prostaglandin E1 (5 ng) and ADP (20 μg)-coated membrane (Innovance PFA P2Y; Siemens Healthcare, Marburg, Germany), although this is not available worldwide. For each cartridge, whole blood (usually 800 μl) is placed into the sample reservoir, and the sample aspirated under a constant vacuum, passing with high shear force through a capillary and a microscopic aperture in the membrane. This results in platelet activation, attachment, and aggregation, forming a stable platelet plug at the aperture. The instruments report a 'closure time' (CT), which is the time required for full aperture occlusion and cessation of blood flow.

The instruments are very sensitive to von Willebrand factor defects/deficiencies, and therefore to VWD (5,13), as well as to severe platelet function defects, including BernardSoulier Syndrome or Glanzman's Thrombasthenia, but only moderately sensitive to mild platelet defects/VWD. The system is also very sensitive to aspirin and can also be theoretically used to study platelet P2Y12-receptor agonists; however, this is not widely utilized. Thus, the current evaluation is of data using C/Epi and C/ADP test cartridges, as applicable to screening VWD, platelet function, and aspirin ingestion.

Proficiency testing/EQA for the PFA-100/200

Geographically based in Sydney (Australia), the Royal College of Pathologists of Australasia Quality Assurance Program (RCPAQAP) reflects an international EQA service covering a wide range of tests (http://www.rcpaqap.com.au/), and has been providing PFA-100 challenges for the past 10 years, with several past reports already published, as last updated in 2014 (12). Challenge samples are specifically designed by one of us (EJF) to mimic test results that would reflect the major scenarios laboratories typically encounter, including (a) normal test patterns (i.e., normal CTs for both C/ADP and C/Epi) and (b) aspirin-like patterns (i.e., greatly prolonged C/Epi CT but normal C/ADP CT), and (c) test patterns consistent with 'primary hemostasis defects' potentially representative of (mild, moderate, or severe) VWD or platelet dysfunction (viz, prolonged CTs with both C/Epi and C/ADP). Participants are required to source ~10 ml of normal whole blood using their standard citrate anticoagulant collection tubes and local collection protocols that yield normal 'baseline' C/ADP and C/Epi CTs. For subsequent challenges, participants carefully pipette whole blood (1.0 ml) into duplicate challenge tubes, cap the tubes and incubate for 15 min, with intermittent mixing, at room temperature. This challenge-incubated whole blood is then tested (within 30 min) with fresh C/ADP and C/Epi test cartridges to generate test-challenge CTs. Participants take note of any error/warning messages/test codes and are also guided on required actions. Results are sent to the RCPAQAP by a designated date for analysis and report generation. In addition to the 'proficiency testing' component (test-challenge tubes), participants are encouraged to provide interpretations of individual C/ADP and C/Epi test results, in addition to an overall 'diagnostics' interpretation. In the current report, we have evaluated data for the PFA-100 and PFA-200 together (last four years; 2014–2017 inclusive) and separately (for the last three data sets, with these representing near equal numbers of participants) to assess for any potential differences.

The numbers of participants for the PFA EQA have risen annually over the past 10 years (12), being 67 in 2017, with geographical distribution as follows: Australia (n = 41), New Zealand (n = 9), South Africa (n = 7), Netherlands (n = 4), Hong Kong (n = 3), and Austria/India/Oman (n = 1 each).

IQC assessment

The same challenges have also been assessed internally (i.e., at the ICPMR laboratory) as potential IQC material. Essentially, the PFA-100/200 manufacturer (Siemens)-recommended procedures for quality control for the PFA-100/200 include daily electronic checks and periodic running of normal blood (e.g., with changes in batch lots of test cartridges or after PFA servicing). The EQA material can act to supplement this process by provision of 'abnormal' CT data, essentially acting as a 'pathological' QC material. Some of this data is also used as part of the 'homogeneity' and 'stability' assessment process for the EQA material.

Results

Table I provides detailed summary data for individual challenges for the past four years of EQA (2014–2017 inclusive), identifying target CTs, scenarios intended to mimic, and median and 95% confidence intervals of results to reflect result ranges, as well as coefficients of variation (CVs) to indicate cross-laboratory reproducibility. Data is also displayed in Figure 1A (C/Epi) and 1B (C/ADP) as box plots to show data consistency. Median (range) CTs for challenges are within expectations, according to challenge design scenario or target CTs. Thus, challenges designed to mimic a 'severe primary hemostasis defect' yielded maximally prolonged (>250 s) median CTs for both C/ADP and C/Epi. Participants also generally reported greatly increased CTs (compared to baseline) (Figure 1). Challenges designed to mimic a 'moderate defect' similarly yielded prolonged (>200 s) median CTs for both C/ADP and C/Epi (Table I) and generally increased CTs (Figure 1). Regular challenges reflective of 'no-additive' tubes (negative control or blank challenge tubes) generated similar CTs to baseline (Table I; Figure 1), although slight increments were often observed; we believe this largely reflects the additional

Figure 1. (Continued).
for PFA-100 vs. PFA-200 for last three sample sets tested (as performed in 2017 and early 2018), where nearly equal numbers of participants were available. A statistically significant difference was seen in one baseline comparison, which is perhaps to be occasionally expected as these baseline sets reflect testing of different (i.e., heterogeneous) whole blood samples. However, there was no difference for PFA-100 vs. PFA-200 CTs following any test challenge (either negative or positive challenges). (G) Levey–Jennings-like plot using normal baseline whole blood CT values as 'normal QC' and sequential test data from IQC system sample PF15-08a as 'pathological QC,' reporting CTs in seconds (s; y-axis in each figure), for a theoretical timeline of 12 months. Here, QC limits for the 'normal QC' sample (= baseline whole blood CTs) would be values below the normal/abnormal cutoff value (manufacturer values used in this example). For PF15-08a, representing a 'pathological QC, the QC limit could be assigned as a value above a predefined cutoff (200s used in this example). (H) Data from Figure G, but now expressed in terms of x-fold of baseline. In this potential IQC scenario, the QC limits might be expressed by predefined limits of test data (e.g., above 2×).

sample handling and testing 'delay' arising from the EQA process at each laboratory. Imprecision generated for test challenges is typically similar to or superior to native whole blood (baseline CTs; no-additive challenges), and CVs for most challenges are <20% (Table I).

Interpretations were also generally consistent with expectations and laboratory provided data (Figure 1C). Thus, CTs for non-additive ('negative') tubes were generally reported as normal, and overall PFA interpretation also generally reported as normal. If participants reported occasional abnormal CTs or mild defects, this often correlated with their test data (i.e., CTs above normal cutoff limits, generally slightly). Conversely, for positive challenge tubes, most reported abnormal (prolonged) CTs (for both C/ADP and C/Epi) and abnormal PFA interpretations, with the reported 'abnormality' generally consistent with reported CTs and test patterns.

Increasing numbers of EQA participants have started using PFA-200 instruments in place of older PFA-100 instruments (Figure 1D). Accordingly, we can for the first time show comparative findings between PFA-100 and PFA-200 (Figure 1E [C/Epi] and 1F [C/ADP]). As can be seen, although there was one occasion of a statistically significant difference in baseline readings between PFA-100 and PFA-200, this might be explained because these actually reflect heterogeneous baseline blood samples, albeit all samples being 'normal.' In contrast, EQA data for all test challenges showed no significant differences between PFA-100 and PFA-200. Finally, recent data reflective of the potential IQC-like approach is shown in Figure 1G and 1H. Inter-assay CVs from this IQC data, essentially also representing homogeneity and stability testing for the EQA samples, is similar to that of EQA data (e.g., for PF15-08a, CVs were 19.4% (baseline C/ADP), 15.5% (baseline C/Epi), 6.2% (PF15-08a C/ADP), and 6.4% (PF15-08a C/Epi), respectively).

Discussion

We report updated findings related to EQA for platelet function testing as specifically applied to the PFA-100/200 and for the first time showed comparative data for PFA-100 vs. PFA-200. RCPAQAP Haematology is the only EQA provider worldwide offering such proficiency testing, other than the College of American Pathologists (CAP) program, which briefly reported some findings in 2007 (14). In the CAP report, inter-laboratory PFA CT CVs were identified to be around 20% for baseline CTs, but as high as 30–50% for test challenges. The CVs in our EQA (Table I) therefore seem to be much lower, and similar to those of other specialized assays such as lupus anticoagulant, factor assays, and factor inhibitor assays (15,16) but well below those of some other specialized assays such as anti-cardiolipin and anti-B2-glycoprotein-I (17).

Our report extends findings previously reported by us (12,18–20). The PFA-100/200 globally represent the most widely employed platelet function-screening instruments (1,5) and the transformation from the PFA-100 into the PFA-200 appears to have not affected its performance in the EQA setting. PFA-100/200 EQA test challenges have now been conducted by the RCPAQAP for 10 years and have consistently provided data essentially matching expectations related to their design. Also, reproducibility has been extensively explored and proven by use of similar or identical challenge material across separate exercises (12,18–20).

In conclusion, we update our experience with this EQA for the PFA-100/200, which includes a test-challenge ('proficiency testing') component and report the conceptual IQC use of such EQA material. Although establishing classical processes for EQA and IQC of platelet function is not currently possible, our experience reflects an alternative novel approach to achieving these goals. Such concepts could potentially be adapted to other platelet function screening instruments as well as for classical LTA/WBA. It is also hoped that the range of available test challenges may be expanded, perhaps including stable antiplatelet medication-based challenges.

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Declaration of Interest

The authors have no conflicts of interest to report.

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