

# The Royal College of Pathologists of Australasia Quality Assurance Programs 10 year review of INR

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## Introduction

The international normalized ratio (INR) is a common coagulation assay, primarily utilised to monitor warfarinised patients. The Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP) offers external quality assessment samples for routine haemostasis tests, including INR, eight times per year. A 10 year prospective study (2010 – 2019) study was performed to assess if the introduction of new reagent formulations improved overall INR external quality assurance (EQA) performance over a range of INR results.

## Methods

160 samples were analysed from 80 surveys performed during January 2010 – November 2019 with INR medians ranging from 1.0 – 4.5. Error rates of INR reagents with >20 users were calculated, where an ‘error’ was defined as a result >3 standard deviations (SDs) from the individual reagent mean. The average CV was calculated for all INR medians returned over the past 10 years. Enrolment rates of the major reagents, and their percent increase or decrease from 2010 compared to 2019 were analysed.

## Results

Overall enrolment in the haemostasis program increased 17.1% from 677 in 2010 to 793 in 2019, while individual reagents fluctuated. The most widely used reagent in the program, Siemens Thromborel S, increased by 56.1%, while Siemens Innovin and IL Hemoliance Recombiplastin decreased by 15.8% and 30.0% respectively. Stago’s new PT/INR reagent NeoPTimal is progressively replacing the Stago Neoplastine CI Plus reagent, with enrolment numbers increasing from 0 in 2017 to 155 in 2019, while Neoplastine CI Plus fell from 255 to 80 enrolments in the same period (Figure 1).

Error rates of Stago Neoplastine CI Plus and the Siemens reagents Thromborel S and Innovin are comparable at 1.93%, 1.84% and 1.82% respectively. IL Hemoliance Recombiplastin and Stago NeoPTimal demonstrated lower error rates at 1.44% and 0.81% (Figure 2).

As the INR increases, the results returned have a higher degree of variation (Table 1). At an INR of 1, the average CV over the 10-year period was 5.9%, while an INR of 4.5 returned an average CV of 13.8%. This positively related relationship between INR and CV is demonstrated in Figure 3, where the slope of the regression line is 1.9.

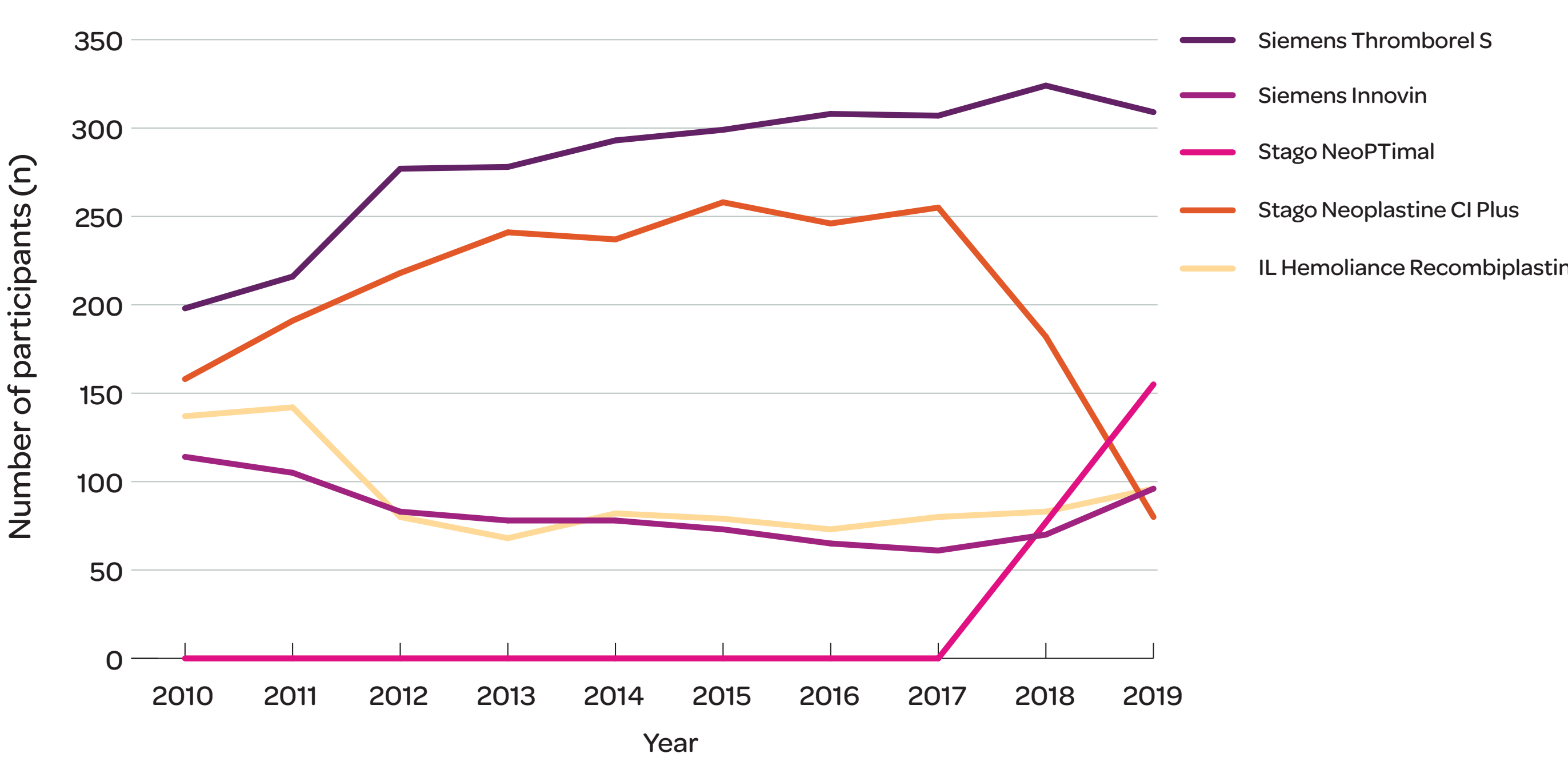


Figure 1. INR Enrolments and reagent types listed for RCPAQAP’s Haemostasis Program (2010-2019)

Table 1. Average Coefficient of Variation (CV) of INR Medians

INR	1	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.3	2.4	2.6	2.7	2.8	3	3.1	3.2	3.6	3.7	3.8	4	4.1	4.2	4.3	4.5
(n)	25	2	2	14	16	1	3	15	14	2	2	3	11	4	6	3	5	5	3	3	3	3	3	4	4	4
CV	5.9	5.9	6.5	6	6.3	6.3	8.7	11.2	11.1	9.8	7.1	6.5	8.7	9	9.5	9.6	9.7	10.6	10.6	11.7	8.8	13.3	13.2	12	14	13.8

## References

1. Stago, STA-NeoPTimal package insert, 2017
2. WHO Technical Report Series, No. 979, 2013

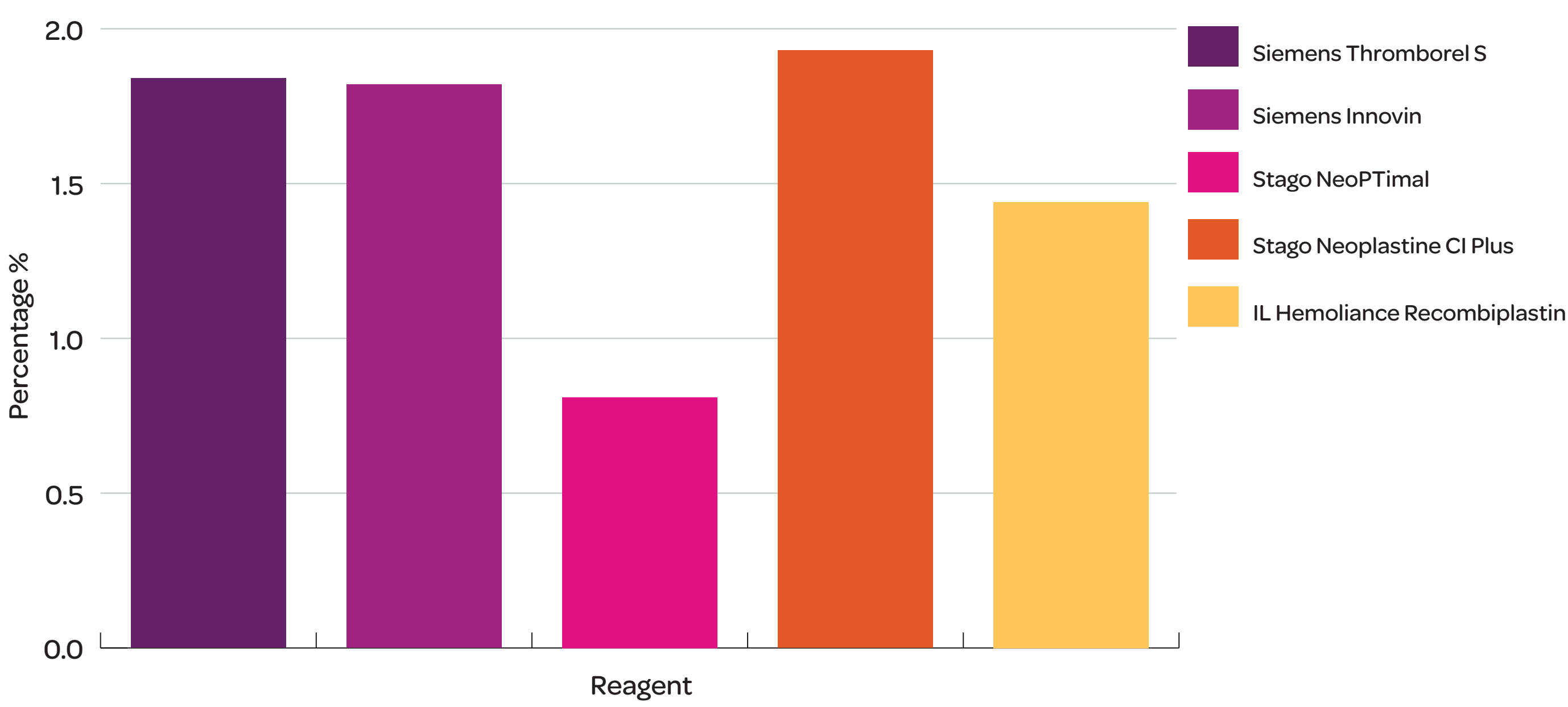
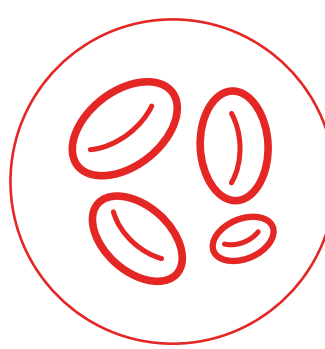


Figure 2. Error Rates of INR Reagents (2010-2019)

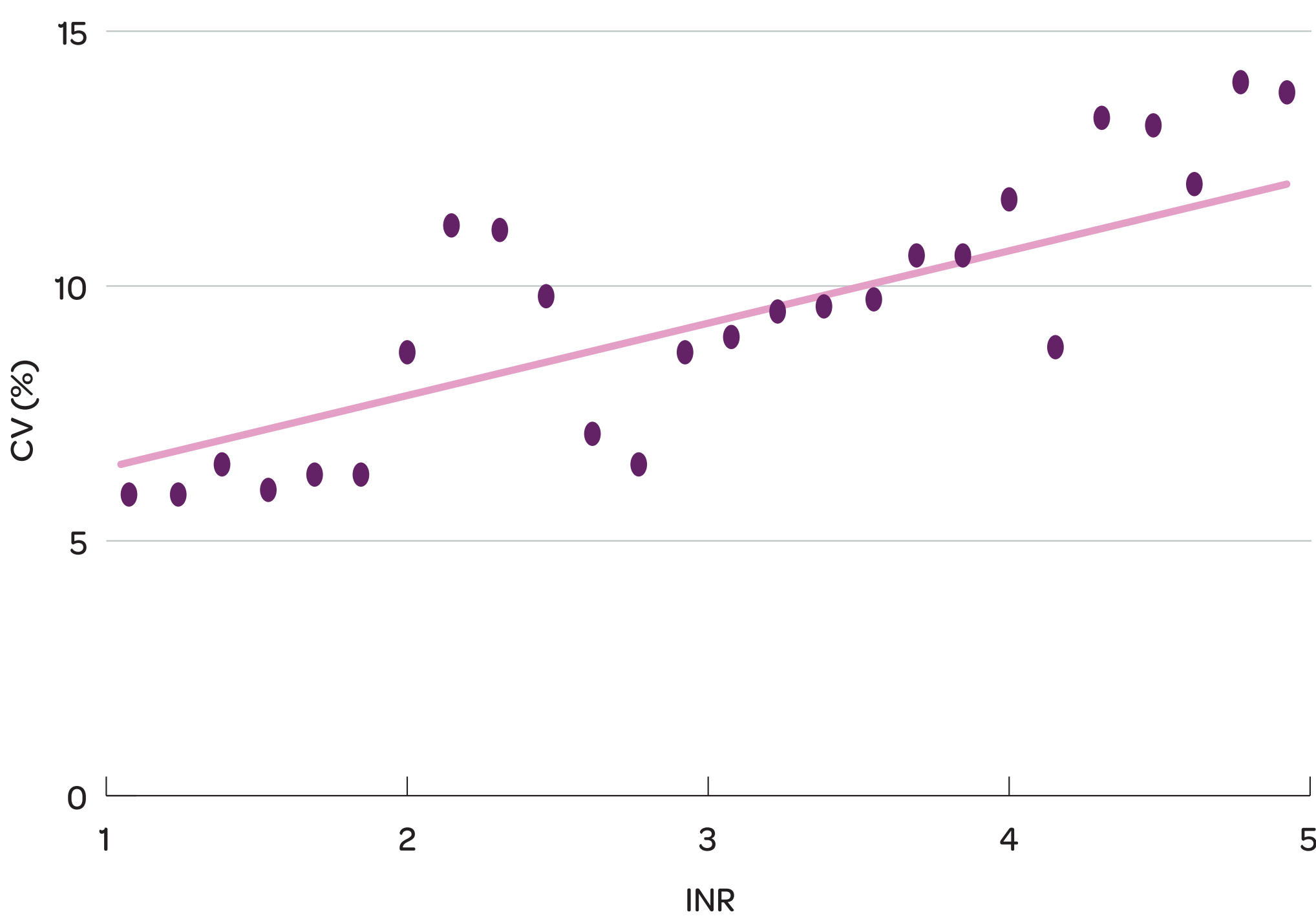


Figure 3. Average Coefficient of Variation vs INR Medians

## Discussion

The 17.1% growth in participants reporting INR results in our haemostasis program from 2010 to 2019 is primarily due to RCPAQAP’s expanding international market. In 2010 27% of users in the haemostasis program were international participants compared to 35% in 2019. The biggest change in reagents came from participants swapping from Stago’s Neoplastine CI Plus reagent to the Stago NeoPTimal reagent as it was rolled out. The NeoPTimal reagent has an improved international sensitivity index (ISI) of 1, which was a major reason for the development of this new reagent<sup>1</sup>. ISIs close to 1 provide more accurate INR results, although international guidelines accept ISIs between 0.9-1.7<sup>2</sup>. Stago’s NeoPTimal reagent had the lowest error rate while Stago’s Neoplastine CI Plus had the highest.

The error rates were calculated from an average of 160 samples, where an error was defined as a result >3 SDs from the reagent mean. All major reagents analysed here had relatively low error rates of <2%. It is also important to note that some errors may have been due to transcription errors i.e. reversed results, or specific to the analyser used.

The relationship between increasing INR and CV is consistent with higher measurement of uncertainty in the pathological ranges, e.g. normal patients have an INR of ~1.0 whereas most warfarinised patients aim for a target INR of ~2.0-3.0<sup>2</sup>.

## Conclusion

The introduction and uptake of improved reagents over the 2010 – 2019 review period was reflected in an associated improvement in EQA performance. Statistics collected around variation of results confirmed that as INR values rise, CV’s also increase.