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Validation and feasibility of a postal system for remote monitoring of HbA1c

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ABSTRACT

Introduction The COVID-19 pandemic has reduced the accessibility to hemoglobin A1c (HbA1c) tests required for virtual diabetes clinics. The aim was to develop and validate a user-friendly postal system for remote HbA1c monitoring.

Research design and methods Validation: A total of 123 capillary blood samples from people with diabetes (PWD) needing face-to-face consultations along with healthy volunteers were measured on a point-of-care (POC) Siemens DCA Vantage Analyzer. Another sample of 5–10 drops was simultaneously collected in a K2EDTA tube (BD Microtainer) and stored for up to 12 days at room temperature for subsequent retesting. Feasibility: During October to December 2020, a total of 286 postal HbA1c kits were sent to PWD prior to their virtual consultation. These contained sample collection guidance, the necessary equipment and a feedback form. As per Packing Instruction 650 regulations, these were posted back to the diabetes center for HbA1c testing on the POC analyzer.

Results There was a strong correlation between the first and the stored sample (R^2=0.978). There was a small clinically insignificant negative bias −1.53 mmol/mol (2 SD = 3.10 mmol/mol). Bland-Altman plots showed 93% of results within 2 SD. Of the 87% of returned kits, only one sample failed to be analyzed. 94% of PWD who provided feedback were happy to use the postal HbA1c system again.

Conclusions A robust user-friendly postal HbA1c system has been created and successfully integrated into clinical practice using the existing POC equipment at the diabetes center. It provides accurate HbA1c results and is an invaluable tool for remote monitoring of HbA1c in PWD—both during and after the pandemic.

Significance of this study

What is already known about this subject?

- Hemoglobin A1c (HbA1c) measurement is an important tool for monitoring glycemic control in people with diabetes (PWD), but unfortunately during the COVID-19 pandemic access to an up-to-date HbA1c measurement for PWD has been challenging.

What are the new findings?

- We describe an inexpensive, simple to implement and accurate system for at-home blood collection, postage and testing; providing accurate HbA1c results for virtual consultations.
- The at-home capillary blood collection system was well received by PWD.
- Our system provides clinicians the opportunity to obtain an up-to-date HbA1c from PWD prior to a virtual consultation.

How might these results change the focus of research or clinical practice?

- Our at-home blood collection system enables PWD to independently collect their blood sample in the comfort of their own home and safely return it to the diabetes center for analysis, thus providing clinicians with this important information prior to remote consultation using virtual telemedicine.

INTRODUCTION

The COVID-19 pandemic has led to a significant number of National Health Service (NHS) clinics being moved from the traditional face-to-face model to virtual consultations using telemedicine. Unfortunately, the need for social distancing and patient-related hesitation to attend healthcare facilities have made it difficult to obtain a hemoglobin A1c (HbA1c) measurement for use at the virtual consultation. Newer technologies such as flash glucose sensing and continuous glucose monitoring are being increasingly used and provide invaluable data for assessing glycemic control. However, for the majority of people with diabetes (PWD), HbA1c remains the critical tool for evaluating glycemic control over a period of 100–120 days.

Remote HbA1c monitoring could potentially provide a solution, and to date a number of blood collection methods have been described, including dried blood spot (DBS) collection, volumetric absorptive microsampling (VAMS) and commercial kits.[1–7] Unfortunately, each has significant issues preventing widespread clinical us. Some have been reported to have inconsistent accuracy,[1] while others involve a lengthy time-consuming process,[2–4] many are economically non-viable and there is a significant lack of feedback from PWD to support their use in routine diabetes care.[5–7]

For a remote HbA1c blood collection system to be adopted successfully into clinical practice, it needs to provide accurate and

reproducible results and needs to be economically viable and user friendly for PWD to collect samples and for NHS staff to process these.

The Diabetes Centre at Ipswich Hospital (East Suffolk and North Essex NHS Foundation Trust) employs two point-of-care Siemens DCA Vantage Analyzers (Siemens Healthcare Diagnostics, USA) which provide reliable HbA1c results within 6 min. Use of the analyzers in parallel increases sampling throughput. These analyzers have been in routine use in our diabetes center for over 20 years and are widely available in clinics throughout the UK.

The aim of this article is to describe how we developed an inexpensive, effective system for home collection and postal return of capillary blood samples for remote HbA1c measurement; and to determine the validity of the HbA1c results where the postal system results in a delay in its measurement.

METHODS

Initial concept testing: handling of capillary samples and accuracy testing following storage up to 12 days

For the postal HbA1c blood collection system to be considered effective, three important criteria had to be fulfilled: first, it was necessary to demonstrate that the samples assessed after a period of storage (due to postal transit) could still be processed by the Siemens DCA Vantage analyzers and analytical quality maintained. Second, the method needed to comply with specific postal regulations and, finally, there needed to be good uptake and acceptance by PWD.

A total of 123 capillary blood samples were collected from both, consenting PWD (n=94) attending the diabetes center for face-to-face consultations and healthy volunteers (HV) (n=29). The latter were colleagues from the Ipswich Hospital. One microliter of capillary blood was collected by laboratory staff at the Ipswich Diabetes Centre into the capillary tube supplied with the DCA cartridge and immediately tested on the Siemens DCA Vantage Analyzer (Siemens, UK) as per standard procedures. Thereafter, both PWD and HV were asked to follow a photographic guide and collect approximately 50–100 µL blood (~5–10 drops) for retesting after storage at room temperature up to 12 days later. The first 33 samples were collected into CB 300 EDTA tubes (Sarstedt, Germany), and after storage were remixed using a mixer (Coulter, USA) for 6 min. Remixed samples were pipetted (Gilson Pipetman P200, USA) and then dispensed onto the non-absorbent side of Benchkote hydrophobic paper (Whatman, USA) to aid the ease of filling of the DCA capillary tube. Two expected errors on the DCA analyzer are 'High Hb' E107 and 'low Hb' E104; these are known to occasionally occur during routine use but were much more frequent with the 'stored' samples. We speculated that the method we had used did not adequately resuspend the red cells in the separated plasma. Furthermore, as PWD found it difficult to use the Sarstedt tubes which rely on capillary fill we considered alternatives. We turned to K2EDTA BD Microtainer collection tubes (BD, UK) which are filled by scooping capillary droplets. Initial use suggested this was easier for patients, so this was used in subsequent evaluations (n=90). We also abandoned the Coulter remixer in favor of a vortex device (Iswix variable speed vortex, Alpha Laboratories, UK) for 30–60 s at 1400 rpm.

This strategy all but eliminated E107 and 'low Hb' E104 errors. On the very rare occasion when a high Hb E107 error occurred, we found that adding 7 µL saline to the stored sample and remixing using the vortex overcame the problem. All stored samples were tested on the same DCA Vantage Analyzer as their first HbA1c test to prevent any interdevice bias. The performance of the DCA Vantage Analyzers was assessed daily using reconstituted control fluids (Siemens DCA, USA) before testing HV or PWD samples.

Temperature validation study

A further temperature validation study has been conducted to examine the effect of blood sample storage at higher ambient temperature. Seventeen random samples (nine HV and eight PWD) were collected and initially tested as above. The samples were then stored at 29.7°C±0.69°C (EL-USB-2-LCD+RH/Temp Data Logger, Lascar Electronics, UK) for 24 hours, and thereafter retested on the same DCA analyzer.

Postal method for HbA1c collection

The aim was for PWD to collect blood samples independently at home and post them back to the diabetes center for processing.

Three factors were considered to establish a blood sample return system that was reliable and cost-effective:

- Compliance to postal regulations (Packing Instruction 650: the European Agreement concerning the International Carriage of Dangerous Goods by Road[8 9]) (online supplemental data 1).
- Cost-effectiveness of the postal process (online supplemental data 2).
- Convenience/user-friendly nature of the entire process for PWD.

Patient engagement and feedback on the postal HbA1c kits

Once the accuracy of the stored samples was demonstrated and postal requirements were confirmed, we evaluated the acceptability of the system in PWD requiring an HbA1c prior to their virtual consultation. During October to December 2020 a total of 286 kits were sent out. The postal HbA1c kits contained a covering letter explaining why a postal HbA1c was required, a photographic blood collection guide, a packaging guide and a feedback form (online supplemental data 2). The kits also contained the necessary equipment to collect the capillary sample, to package it and send it safely back to the diabetes center according to Packing Instruction 650 regulations.

Table 1 Mean (±SD) HbA1c of samples for both people with diabetes (PWD) (n=94) and healthy volunteers (HV) (n=29) on the day of collection and up to 12 days after sample collection

HbA1c (day of collection)	Total samples (n)	Mean (±SD)	HbA1c (at second analysis up to 12 days)	Mean (±SD)
PWD	94	65 mmol/mol±15.46	94	63 mmol/mol±15.10
HV	29	33 mmol/mol±4.65	29	33 mmol/mol±4.45

P≥0.05: not significant.
HbA1c, glycosylated hemoglobin A1c.

Feedback forms were included with each postal HbA1c kit. All feedback was optional and was related to the use of the of K2EDTA BD Microtainer bottles (BD).

Statistical analysis

Statistical analysis was performed using SPSS V.22 (IBM SPSS Statistics for Windows) and StatsDirect V.3 (StatsDirect, Cheshire, UK). HbA1c as quantitative variables is expressed as mean+SD. The accuracy between samples for both PWD and HV on the day of collection and up to 12 days after sample collection was estimated using first paired samples t-test for mean and then correlation was tested using the Pearson correlation method (significant was defined as p<0.05). To further test the agreement between both sets of sample, we used the Bland-Altman limits of agreement (BA LoA) method using X-axis as mean of both HbA1c sets and Y-axis as the difference between both measurements.

RESULTS

Stability results

Table 1 depicts the mean (±SD) HbA1c on the day of collection and up to 12 days later.

The mean (±SD) HbA1c for PWD on day of collection was 65 mmol/mol (8.1%) and 63 mmol/mol (7.9%) when retested up to 12 days later with no significance noted (p>0.05). Similarly, for HV, no significance was noted on day of collection (33 mmol/mol 5.4%) when compared with the retest (33 mmol/mol 5.4%); p>0.05. Intervals between initial HbA1c testing and stored sample HbA1c testing are shown in table 2.

Figure 1 shows the Pearson correlation between the first and the stored HbA1c samples. A strong correlation coefficient of R^2=0.975; p<0.001 was observed between both samples. This suggests that both sample sets had a significant positive relationship with one another but this may not necessarily depict agreement.

To test the latter, we used the BA LoA method as shown in figure 2. The LoA for the BA plots were set at mean +1.96 SD and mean −1.96 SD. It shows that there was a significant agreement between both sets of results for both PWD and HV and 93% of results within 1.96 SD of the line of bias.

Temperature validation studies involving 17 random samples (nine HV and eight PWD) which were stored at a higher temperature (29.7°C±0.69°C for 24 hours) and then retested did not adversely affect the accuracy of the methodology. The mean (±SD) HbA1c on the day of collection was 47 mmol ±15.87 as compared with 45.7 mmol ±15.69 when retested 24 hours later (paired t-test: p=0.021). Furthermore, there was a strong positive correlation between the first samples and the stored samples (R^2=0.98) (online supplemental data 5).

Based on the statistical derivations above, we infer that in both PWD and HV, even when the HbA1c was tested

Table 2 Total number of capillary samples tested for stability from healthy volunteers and people with diabetes (n=123). The storage intervals used before the second HbA1c test are shown

Number of days between sample collection and second HbA1c test	Samples (n)
1–2	10
4–7	97
10–12	16
Grand total	123

HbA1c, glycosylated hemoglobin A1c.

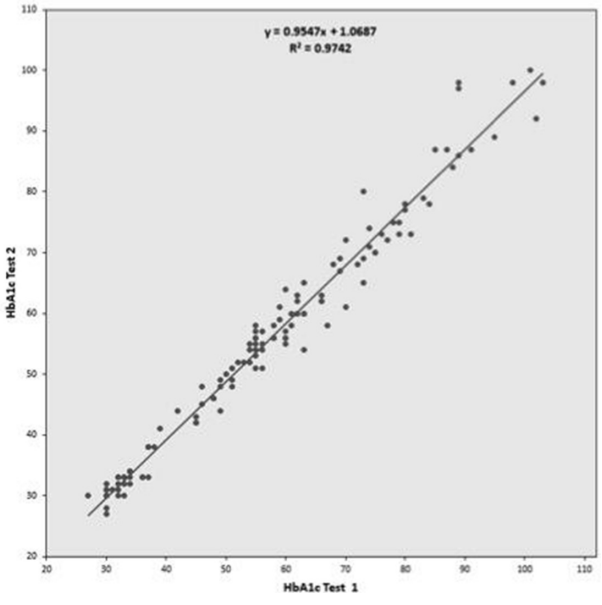

Figure 1 Pearson correlation coefficient for both sample sets of blood. HbA1c test 1 on X-axis indicates samples taken on day of collection and HbA1c on Y-axis indicates retest results up to 12 days later. HbA1c, glycosylated hemoglobin A1c.

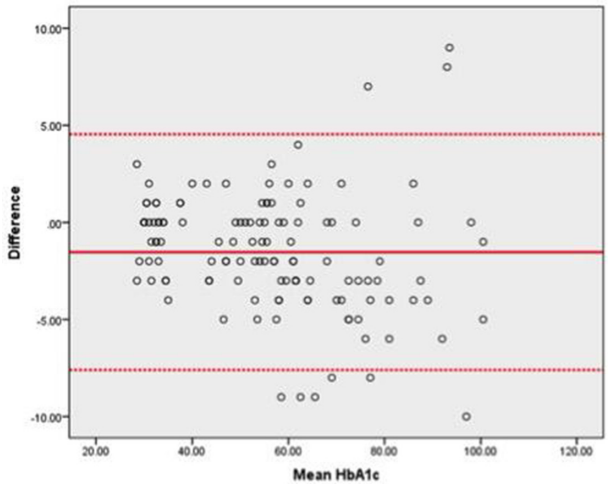

Figure 2 Bland-Altman plot with limits of agreement (LoA) for capillary blood sample HbA1c. The upper LoA has been set at mean+1.96 SD and lower LoA set at mean −1.96 SD. HbA1c, glycosylated hemoglobin A1c.

using the postal system and in different time frames of up to 12 days, there was significant correlation and agreement between both sets of results.

Compliance—return rates

During October to December 2020, a total of 286 kits were sent out to PWD requiring an HbA1c prior to their virtual consultation (age range 9–86 years, mean age 51 years, table 3).

Mean HbA1c for the returned kits was 67 mmol/mol (8.3%) (range 31–128 mmol/mol; 5.0%–13.9%). Nine returned samples were >126 mmol/mol (>14.0%) and 29 samples were above 97 mmol/mol (11.0%).

Of the 210 returned kits (73%), there was only one sample that failed to be analyzed. There were four samples that produced an error but were successfully retested as described in the Methods section. All four errors were expected errors of E107 (high Hb) (n=2) or E104 (low Hb) (n=2).

Of those who did not provide a sample, there were several reasons for not doing so, including no need as already had a recent HbA1c, being out of the country, and deferring their appointment. There were also some very frequent non-attenders who were unlikely to engage. If these were not considered the return rate was 87%.

Table 3 Demographics of people with diabetes (PWD) using the postal HbA1c, October to December 2020

		Age (years)		
	n	Mean	Minimum	Maximum
Women	102	54	19	86
Men	175	52	19	8
Children (9–18)	9	15	9	18
Total PWD	286	51	9	86

HbA1c, glycosylated hemoglobin A1c.

Feedback

Feedback was received from 84 of the 210 who returned a sample (40%). The postal HbA1c was well received with 94% agreeing that they would use it again (online supplemental data 3).

As expected, collecting the capillary sample proved to be the main problem but although 17% found it very difficult (online supplemental data 3), approximately half of these would still use the system again.

Notably, some feedback mentioned that the addition of an online video guide would be beneficial to aid sample collection.

Cost

The cost of the postal HbA1c kit equipment, postage and processing was approximately £2.63 per person, which rose to £3.32 per person when factoring in non-returned kits (online supplemental data 4).

DISCUSSION

The COVID-19 pandemic has made it challenging to obtain an up-to-date HbA1c for PWD prior to their diabetes consultations. At the time of designing our system, a reliable, inexpensive and easily implemented method which was acceptable for PWD to collect their capillary blood samples at home and gave accurate results was lacking.[1–7]

DBS collection devices have been considered a possible solution. However, in practice they require multiple, time-consuming processing steps in addition to a final calibration to obtain an HbA1c value.[1–4 6 7] The storage, processing and calibration steps are not standardized, despite many efforts to achieve this and there are conflicting reports of their accuracy.[1] A universal calibration formula for DBS was proposed by Affan *et al*[1]; however, Mastronardi *et al*[6] discovered that this correction formula was unfortunately not applicable to their study DBS results.

Despite only requiring a small amount of blood, DBS may not be an easier alternative to whole capillary blood collection for PWD, as insufficient sample rates of up to 15% have been reported.[7] Although Fokkema *et al*[3] produced excellent PWD feedback and accurate results from PWD using DBS, this has not been replicated in other studies. One such study reported home-collected samples were significantly different from the result of the laboratory-collected samples (Hall *et al*).[4]

A review of DBS studies has shown that HbA1c can only be accurately measured within a narrow range[1] and is thus not suitable for those with poorer control.

VAMS technology is an alternative blood collection method, but unfortunately the processing and calibration steps are still lengthy and complicated. Although there are some data on the use of VAMS over a range of HbA1c levels,[2] the device and additional equipment required to process the sample are still expensive, limiting its clinical use.[5]

The postal HbA1c system that we have devised solves many of these issues: it is standardized, requires minimal processing, is relatively inexpensive and the HbA1c result is available directly from the Siemens DCA that is locally used and already in place. Our postal HbA1c was shown to be accurate, maintained sample stability for up to 12 days and produced clinically acceptable results. The sample stability time frame allows for any postal delays that may occur over holiday periods and indeed occurred during the pandemic.

Other studies have shown that HbA1c measurements are stable using a Siemens DCA analyzer in samples stored for up to 14 days and up to 21 days using affinity chromatography at room temperature,[10 11] thus mirroring our results. It has been suggested that sample stability may reduce at temperatures over 30°C[10]; however, in the UK, room temperatures seldom exceed this, and of note our accuracy study was undertaken during the summer months in non-air-conditioned rooms. This is further supported by our temperature validation data which demonstrated that an increase in temperature, which may occur during postage, did not significantly affect the stability of the results. A recent paper by Beck *et al*[12] has also shown that an increase in temperature during postage of samples (up to 40.6°C) did not adversely affect the stability of the results.[12]

The return rate of 73% was acceptable and could be improved if the referral process identified those in whom a home measurement is appropriate. Since completion of this study, and between January and March 2021, the return rate for 245 kits has improved to 80%.

Although only 40% provided feedback, it was optional. Also, the study was done during the COVID-19 lockdown period and could have affected the feedback response rates; however, 94% of those responding were willing to use the system again.

As expected, PWD found physical collection of blood a challenge with 17% reporting finding this difficult; despite this the majority were willing to use the kits again. Difficulty in sample collection has also been encountered in DBS studies with 33.3% finding it difficult to apply blood to the DBS device.[4]

To make the sample collection easier, we have subsequently reduced the amount of blood required from 10 to 5 drops (from 100 to 50 µL). Sample collection may also be improved by the laboratory staff at diabetes center demonstrating the method when the PWD attends for phlebotomy for their face-to-face appointment and also by access to an online video which we are producing.

The evaluation involved a cohort of PWD with a wide range of HbA1c levels (31–128 mmol/mol, HbA1c 5.0%–13.9%). The simplicity of this system has facilitated its easy integration into the activity at the diabetes center's mini-laboratory and although this study was confined to patients attending a diabetes center it could be easily adopted for use in other diabetes care settings. The equipment required for processing is minimal, user friendly, requires little training and is cost-effective. Health economics has not been calculated for other home collection systems,[4] whereas we have shown that the economic impact of this project is minimal with an estimated cost of £3.32 per person (online supplemental data 4). This cost includes non-returned kits, the number of which could be reduced by more stringent PWD selection, potentially bringing the cost to between £2.50 and £3.00 per person.

Since designing and testing our methodology a paper has been published which assessed two capillary blood collection kits for the measurement of HbA1c in the USA.[12] Similar to our methodology, the kits were well received by PWD and both kits showed accurate, reproducible results up to 10 days, strengthening our findings. However, the blood samples were collected in clinic and so return rates and patient engagement in a non-controlled environment were not assessed, as were in our paper.

There are a number of limitations to consider for our system. Only the Siemens DCA Vantage Analyzer was used since it is already available in our laboratory; however, we see no reasons why similar results would not be obtained on other analyzers. A further limitation is the evaluation being only undertaken at one center. Again, we see no reasons why other centers could not replicate the results and obtain similar patient engagement. Finally, we have only tested samples stored for up to 12 days. Significant postal delays and laboratory closures during the weekends could delay testing to beyond this time, although this was not the case with any of our samples nor during the recent Christmas and the New Year period.

CONCLUSIONS

In conclusion, we describe an inexpensive, simple to implement and accurate method for obtaining HbA1c results for remote clinics which has good patient acceptance, and overcomes the many challenges that have hampered DBS and VAMS blood collection. We believe that in addition to necessary face-to-face consultations, virtual consultations supported by remote HbA1c testing such as described will be a significant advance in diabetes care.

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Contributors All authors were involved in the writing of the manuscript. JC planned and completed the laboratory work for the validation studies, designed the postal HbA1c system, collected the data and integrated the postal HbA1c system into the diabetes center clinics. SS completed the statistical testing of the data and had an editorial role for the manuscript. WGJ provided technical advice. GR is guarantor for the article, conceived the concept of the postal HbA1c system, and provided technical advice for the validation studies and support for the manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was designed and carried out during the peak of COVID-19 pandemic activity in the UK. During this period, the urgent necessity for an alternate method of remote glycemic monitoring was considered to be of

utmost clinical importance. Hence, urgent ethical considerations for this study were reviewed and ratified by the following institutional board: Diabetes Trials Unit at Ipswich Hospital and supported by R&D at Ipswich Hospital, East Suffolk and North Essex NHS Foundation Trust, so that it could be adopted early in clinical practice. In view of the same clinical reasons, it was deemed that submission to formal NRES Ethics Committee adjudication was not necessary due to COVID-19-related delays. All PWD and healthy HV gave informed consent before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information.

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REFERENCES

1 Affan ET, Praveen D, Chow CK, *et al*. Comparability of HbA1c and lipids measured with dried blood spot versus venous samples: a systematic review and meta-analysis. *BMC Clin Pathol* 2014;14:1472–6890.
2 Verougstraete N, Lapauw B, Van Aken S, *et al*. Volumetric absorptive microsampling at home as an alternative tool for the monitoring of HbA1c in diabetes patients. *Clin Chem Lab Med* 2017;55:462–9.
3 Fokkema MR, Bakker AJ, de Boer F, *et al*. HbA1c measurements from dried blood spots: validation and patient satisfaction. *Clin Chem Lab Med* 2009;47:1259–64.
4 Hall JM, Fowler CF, Barrett F, *et al*. HbA_{1c} determination from HemaSpot™ blood collection devices: comparison of home prepared dried blood spots with standard venous blood analysis. *Diabet Med* 2020;37:1463–70.
5 Rudge J. Using remote blood collection with VAMS to accurately measure HbA1c in diabetes. Neoteryx 2020, 2020. Available: https://www.neoteryx.com/hubfs/Content/Technical%20Briefs/HbA1c-Tech-Review-v5.pdf [Accessed Mar 2021].
6 Mastronardi CA, Whittle B, Tunningley R, *et al*. The use of dried blood spot sampling for the measurement of HbA1c: a cross-sectional study. *BMC Clin Pathol* 2015;15:13.
7 Jones TG, Warber KD, Roberts BD. Analysis of hemoglobin A1c from dried blood spot samples with the Tina-quantR II immunoturbidimetric method. *J Diabetes Sci Technol* 2010;4:244–9.
8 Department of Transport. Guidance: packaging and transport requirements for patient samples-UN3373. Gov.uk 2020, 2020. Available: https://www.gov.uk/government/publications/packaging-and-transport-requirements-for-patient-samples-un3373/packaging-and-transport-requirements-for-patient-samples-un3373 [Accessed Mar 2021].
9 Royal Mail. Prohibited and restricted items 2019, 2019. Available: https://personal.help.royalmail.com/app/answers/detail/a_id/96/kw/prohibited%20items [Accessed Mar 2021].
10 Rohlfing CL, Hanson S, Tennill AL, *et al*. Effects of whole blood storage on hemoglobin A1c measurements with five current assay methods. *Diabetes Technol Ther* 2012;14:271–5.
11 Little RR, England JD, Wiedmeyer HM, *et al*. Glycosylated hemoglobin measured by affinity chromatography: micro-sample collection and room-temperature storage. *Clin Chem* 1983;29:1080–2.
12 Beck RW, Bocchino LE, Lum JW, *et al*. An evaluation of two capillary sample collection kits for laboratory measurement of HbA1c. *Diabetes Technol Ther* 2021;23:537–45.

Supplementary data 1

Compliance to Postal Regulations

The European Agreement concerning the International Carriage of Dangerous Goods by Road (P650) regulates the transport of biological substances. There are four stages of the regulations that need to be considered before sending a sample via post; Classification, packaging, labelling and transport.

A capillary blood sample is considered to be a UN3373 Biological Substance Category B (HSE, Health and Safety Executive) and so has a specific set of rules that govern its transport. The Department of Transport has a comprehensive document that outlines these specific requirements including details of transporting liquid substances that meet Packing Instruction 650 regulations (Department of Transport, March 2020).

The combination of these factors led to the following packaging for the blood samples

(a) Primary receptacle –Leakproof Microtainer Tube (BD Microtainer® K2EDTA, BD, UK)
(b) Secondary Packaging- sealable Biohazard bag (NHS pathology supplies) containing an absorbent pad (absorbent pad, Alpha Laboratories, UK). This was then wrapped in bubble wrap for cushioning
(c) Outer rigid Packaging – Sealable tamper proof cardboard box (PiP Large Letter Quick Seal Postal Boxes, UK Packaging.com, UK) (dimensions 152mmX107mmX20mm)
(d) UN3373 Label (designed and printed on site)

The Department of Transport P650 Guidance 2020 states that the sample packaging is required to be capable of withstanding a drop test of 1.2m, where no substance leaks from the primary receptacle. This integrity of the proposed packaging was tested and met this standard.

References

Department of Transport. Guidance: Packaging and transport requirements for patient samples-UN3373. Gov.uk 2020 https://www.gov.uk/government/publications/packaging-and-transport-requirements-for-patient-samples-un3373/packaging-and-transport-requirements-for-patient-samples-un3373. Published 26 March 2020. Accessed March 2021.

Health and Safety Executive. Transportation of infectious substances. https://www.hse.gov.uk/biosafety/blood-borne-viruses/transportation-of-infectious-substances.htm. Accessed March 2021.

Supplementary data 2

Cost Effectiveness of Postage

Courier systems and the Royal Mail special delivery service were considered for the return of the collected Postal HbA1c samples. However, they are both costly, with the latter quoting £5.70 per item sent back plus an annual fee of £140 +VAT.

An alternative was to use the normal Royal Mail post. According to the Royal Mail prohibited and restricted items, Biological substances category B are allowed to be sent in the post at the specific request of a qualified medical practitioner (Royal Mail, 2019).

This was a significantly cheaper option, costing £0.77 for second class postage out via the hospital post room and £1.15 for 1st class large letter return, totalling £1.92 per person.

To aid with the packaging and postal process a photographic step by step packaging guide was created to show them how to easily package their sample safely, whilst complying with Packing Instruction P650 regulations and the Royal Mail.

References

Royal Mail. Prohibited and restricted items 2019. https://personal.help.royalmail.com/app/answers/detail/a_id/96/kw/prohibited%20items. Published 2019. Accessed March 2021

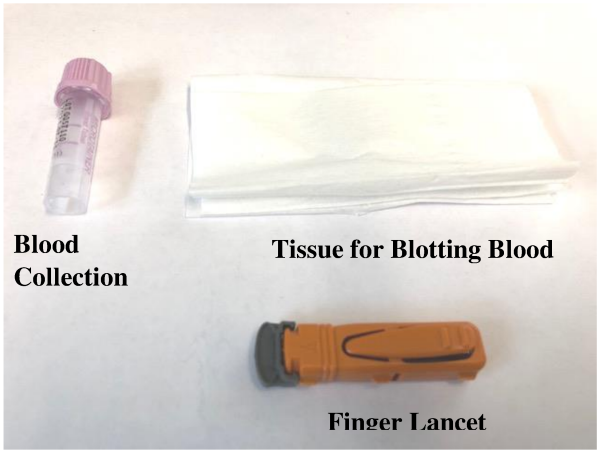
Blood Collection and postal guides (versions used after the pilot)

How To Collect The Blood Sample For Your HbA1c

This process will take no more than 5 minutes of your time

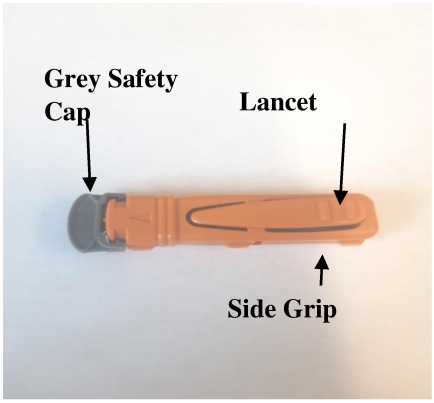
Please note only a small sample of blood is required

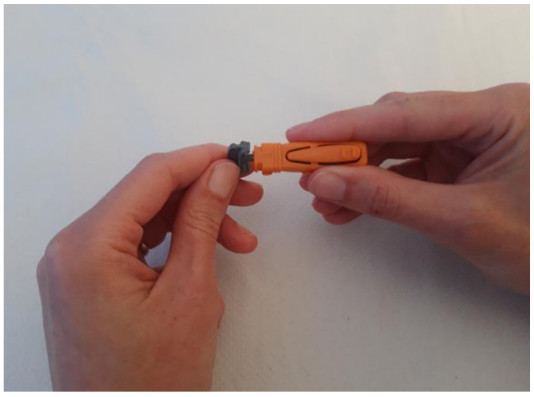
1. On a clean surface, lay out the Blood Collection bottle, tissue and Finger Lancet as shown below.
2. To increase blood flow to the fingers warm your hands by immersing them in a basin of hot/warm water for a few minutes. Dry your hands thoroughly
3. To open the Blood Collection Bottle, grip, twist and pull the purple cap off. Stand the bottle upright with the cap next to it.



Open, Upright Blood Collection Bottle

4. The Finger Lancet is shown below



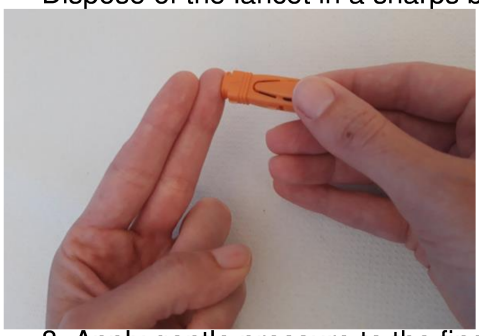


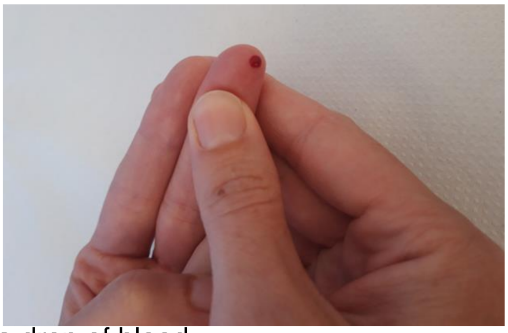
5. Hold the **sides** of the lancet firmly in one hand as shown.

TAKE CARE NOT TO TOUCH THE LANCET TRIGGER ON THE TOP.

6. Twist the grey safety cap **two full turns** and then pull the cap away from the Lancet.

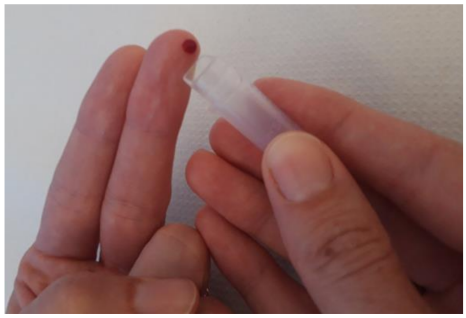
7. Press the open end of the lancet against the finger you wish to prick. Only then do you press the lancet trigger down to release the lancet to prick the finger. Dispose of the lancet in a sharps bin.

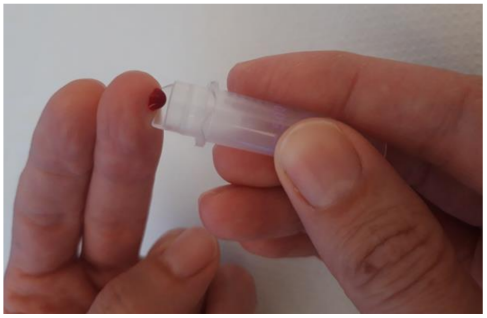




8. Apply gentle pressure to the finger to form a drop of blood.

9. Press the **scoop** of the Blood Collection Bottle against your finger, **just below** the drop of blood. Either let the blood flow into the bottle or move your finger across the scoop, to drop the blood into the bottle. Repeat squeezing and scooping until the **bottle is filled up to the BLACK LINE ON THE BOTTLE (approximately 5 drops).**





10. If the blood smears on your finger, it will not enter the bottle. If this happens, take a tissue, wipe away the blood from the finger, squeeze the finger to form another droplet of blood and **repeat step 9.**

11. Once the Blood Collection Bottle is **filled up to the BLACK LINE (approximately 5 drops of blood)** take the purple lid and **firmly push** it onto the Blood Collection Bottle until you hear a **'click'**. Tip the bottle upside down **twice**, to mix the blood sample. **There is no need to fill the bottle to the top.**

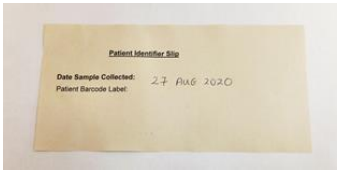
Please note: If you only manage to collect less than 5 drops of blood, please still send the sample to the Diabetes Centre.

Black arrows show that the blood is filled up to the black line

How To Package Your Blood Sample

This guide will help you to post your blood sample back to the Diabetes Centre.
Please read through the following instructions carefully.

1. Write the date that you collected the blood sample on the patient identifier slip—as shown.



2. Then attach one of the two barcode labels.

3. Stick the other barcode label onto the bottom of the biohazard bag.

4. Now put the absorbent pad into the biohazard bag.

5. Next put the lilac coloured tube in which you collected your blood sample into the biohazard bag.

Continue onto the next page...

6. Seal the biohazard bag by pressing **firmly** along the whole length of the grip-seal closure.

7. Place the biohazard bag on top of the bubble wrap and fold the bubble wrap around the bag.

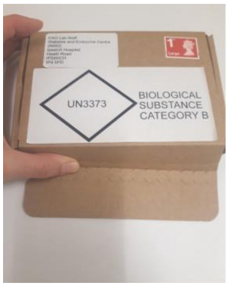
8. Put the bubble wrapped biohazard bag into the cardboard box provided.

9. **<u>It is essential that you put the patient identifier slip with the attached barcode into the cardboard box.</u>** If you would like to leave a feedback comment, this can be written on the feedback form. Please fold the feedback form and put it into the box.

Continue onto the next page...

10. Close the lid of the cardboard box by folding over the top flap of the cardboard box as shown.

11. Press the top flap against the box as shown. Turn the box upside down.



12. Peel off the white sticky tape to expose the adhesive glue.

13. Press the top flap down firmly against the bottom of the box.

14. The box is sealed with your sample inside. Please take it to your local **Post Box** for postage.

(hands photographed in the guides are the authors hands and not patient hands)

Cover Letters- Ad Hoc Letter and Appointment Letters

Diabetes & Endocrinology
Ipswich Hospital
Heath Road
IPSWICH IP4 5PD
(NO 52)
Tel: 01473 704180
Email: ihn-tr.IpswichDiabetesCentre@nhs.net

Dr C Parkinson BSc (Hons) MB ChB FRCP
Dr P D Fowler DM FRCP
Dr D Morris PhD FRCP
Prof G Rayman MD FRCP
Dr S Sharma MD FRCP FHEA

NHS No <NHS number>
14 November 2021

Private & Confidential
<Patient Name>
<Patient Address>

Dear <Patient Name>

Your Diabetes clinician has requested that you have an up to date HbA1c test. To be in line with social distancing measures outlined by the UK government, we have introduced a **finger-prick home blood collection** system. This is so that you do not have to travel to the Diabetes Centre for the test.

With this letter you will find

- The necessary equipment to help you collect a small blood sample at home
- Simple instructions on how to collect the sample
- Pre-paid Packaging Material for sending the sample back to the Diabetes Centre, Ipswich Hospital

Please take some time to carefully read through the instructions before attempting to collect the blood sample, as it is different from the normal finger prick method that you may use for your diabetes monitoring.

Please collect and return your sample within 48hours of receiving this letter

Please note: To maintain accuracy it is important that you **return** the completed sample bottle **as soon as possible. Ideally, please return the blood sample on the same day as sample collection**

If you are experiencing any difficulty and are unable to obtain a sample please contact the diabetes centre on 01473 704180 and we will make alternative arrangements for your blood test
Yours sincerely,

Professor Gerry Rayman

MD, FRCP, MBEClinical Lead for Diabetes

Consultant Diabetologist

NHS No <NHS number>

14 November 2021

Private & Confidential
<Patient Name>
<Patient Address>

Diabetes & Endocrine Centre
Ipswich Hospital
Heath Road
IPSWICH
IP4 5PD

Tel: 01473 704180

Dr P D Fowler DM FRCP
Dr D Morris PhD FRCP
Dr C Parkinson BSc (Hons) MB ChB FRCP
Prof G Rayman MD FRCP MBE
Dr S Sharma MD MRCP FHEA

Dear <Patient Name>

The majority of our clinics are now being conducted by telephone or video-consultation because of COVID-19 and social distancing measures outlined by the UK government.

For your next appointment where only an HbA1c blood test is required* we have introduced a **finger-prick home blood collection** system so that you do not have to travel to the Diabetes Centre for the test.

With this letter you will find

- The necessary equipment to help you collect a blood sample at home
- Simple instructions on how to collect the sample
- Pre-paid Packaging Material for sending the sample back to the Diabetes Centre, Ipswich Hospital

Please take some time to carefully read through the instructions before attempting to collect the blood sample, as it is different from the normal finger prick method that you may use for your diabetes monitoring.

Please collect and return your sample within 48hours of receiving this letter

Please note: To maintain accuracy it is important that you **return** the completed sample bottle **as soon as possible. Ideally, please return the blood sample on the same day as sample collection**

If you are experiencing any difficulty and are unable to obtain a sample please contact the diabetes centre on 01473 704180 and we will make alternative arrangements for your blood test

*Please note: For annual review appointments where additional blood and urine tests are required these will be undertaken at the Diabetes Centre with appropriate shielding of staff and patients. You will be sent an appointment to have this done just prior to your annual review date.

Yours sincerely,

Professor Gerry Rayman

MD, FRCP, MBEClinical Lead for Diabetes

Consultant Diabetologist

Supplementary data 3

People with Diabetes Feedback

Supplementary Table 1 People with diabetes (PWD) feedback for the postal HbA1c. 84 PWD provided feedback out of 210 returned kits (286 kits sent out). Point 5 shows the adjusted feedback for question 4 (79 PWD), where 5 PWD have been removed from analysis. The 5 PWD that were removed was due to; 2 PWD changing their feedback to a positive response, 1 PWD was not suitable for a postal HbA1c for medical reasons and 2 PWD needed education

	Feedback Question	Positive response	Negative response	No Answer
1.	How easy was it to follow the instructions for collecting the blood sample?	**89%** (55% very easy, 34% easy)	**7%** (5% somewhat difficult, 2% very difficult)	**4%**
2.	How easy was it to collect the blood sample?	**82%** (29% very easy, 27% easy, 26% somewhat difficult)	**17%** (17% very difficult)	**1%**
3.	How easy was it to follow the instructions for the packaging and postal?	**92%** (50% very easy, 42% easy)	**7%** (0% very difficult, 7% somewhat difficult)	**1%**
4.	Would you be happy to use the postal HbA1c blood collection system again?	**89%** (37% strongly agree, 36% agree, 17% neutral) Adjusted rate 94%	**10%** (9% disagree, 1% strongly disagree)	**1%**
5.	**Adjusted question 4- Would you be happy to use the postal HbA1c blood collection system again?**	**94%** (39% strongly agree, 37% agree, 18% neutral)	**5%** (1% strongly disagree, 4 % disagree)	**1%**

Supplementary data 4

Costings of the postal HbA1c

The total cost of the postal HbA1c kits was approximately £2.63 per person (Table 2)

The cost of sending out 286 kits was approximately £752.18. The total cost for sending out the 286 kits could be considered to be £952.16 (£752.18 + all non-returned kits £199.88) bringing the cost per person to £3.32

45 kits were expected non-returns, costing approximately £118.35, representing a significant saving that could be made if the referral process could be improved to reduce the number of exclusions.

Supplementary Table 2 Costings for the postal HbA1c kits. Total cost per person is £2.63

Supply name	Number per person	Cost	Cost per 100 patients	Cost per patient	Source	Notes
Unistick 3 extra 21G Lancet	2	£11.27 for 1 box of 200	£11.27	£0.1127	NHS stores, (Owen Mumford, UK)	
K2EDTA BD Microtainer	1	£30.98 for 200	£15.49	£0.1549	BD UK	
Specimen biohazard bag	1	unknown		£0.0000	NHS pathology stores	Alternative used after December 2020
Blood collection guide	1	£0.0118 per print	£1.18	£0.0118	designed on site	
Packaging and postal guide	1	£0.0118 per print	£1.18	£0.0118	designed on site	
Cover letter	1	£0.0059 per print	£0.59	£0.0059	designed on site	
Identifier slip	1	0.0059 for 1 sheet with 3 slips	£0.20	£0.0020	designed on site	
Absorbent pad 125mmX 150mm (100ml)*	1	£94.80 for 500	£9.48	£0.0948	NHS supplies, Alpha Laboratories LTD	Price for each pad cut in half
Labels UN3373**	1	£2.50 for 100 sheets	£0.63	£0.0063	NHS supplies, Nice day label 199.6 X143.5mm	
Label UN3373 print**	1	£0.0059 per sheet	£0.1470	£0.0015	designed on site	4 labels per sheet
Label diabetes centre address	1	£2.48 for 100 sheets	£0.1180	£0.0012	designed on site	21 labels per sheet
Label diabetes centre address to print	1	£0.0059 per print	£0.0280	£0.0003	designed on site	21 labels per sheet
Window Envelope(C4)	1	£5.66 for 250	£2.26	£0.0226	NHS supplies	
Identifier barcode	2	£0.006	£0.084	£0.0008	printed from records	7 people per sheet
Postage Cost	1	2nd class £0.77 + large letter 1st £1.92	£192	£1.9200	NHS supplies, Post Office	Post out via hospital post room
Bubble wrap	1	£11.69	£1.17	£0.0117	NHS supplies, Lyreco UK ITD Stock &BD	
Benchkote	n/a	£96.57 for 50 sheets	£1.680	£0.0168	NHS supplies, Whatman, USA	reduction possible with careful pipetting
PiP large letter postal box	1	500 =£131.28 (vat freepp)	£26.25	£0.2625	UK packaging.com	
Gilson Pipetman P200 ***	n/a	Gifted, usually £209	n/a	n/a	Gilson®, UK	
Gilson Pipetman Diamond Tip D200 Towerpack (960 tips)***	n/a	Gifted, usually £28.40	n/a	n/a	Gilson®, UK	
Iswix Variable speed vortex***	n/a	£290	n/a	n/a	Alpha Laboratories LTD	
Biohazard bag (after December 2020)****	1	£27.00 for 500	£5.40	£0.05	NHS supplies, International Scientific Supplies	

*Price for each pad cut in half, absorbency capacity once pad is cut in half is 50ml

** No cost incurred for printing UN3373 labels after March 2021

***Kindly gifted by University of Suffolk

****Biohazard bag source changed Feb 2021

Supplementary data 5

Temperature validation testing

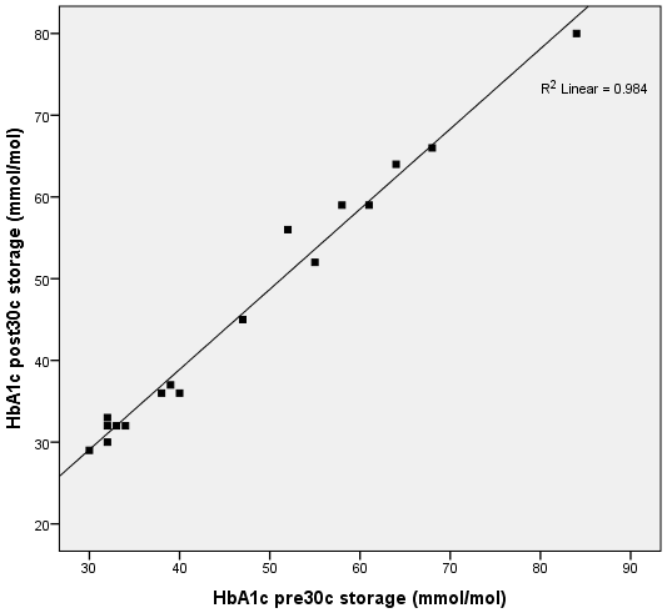
Temperature validation testing was completed to determine if an increase in temperature during postal transit could affect capillary blood sample stability.

Temperature validation studies involving 17 random samples (9 healthy volunteers and 8 people with diabetes) which were stored at a higher temperature (29.7˚C±0.69˚C for 24 hours) and then retested did not adversely affect the accuracy of the methodology. The mean (±SD) HbA1c on the day of collection was 47mmol ± 15.87 as compared to 45.7mmol ± 15.69 when retested 24 hours later (Paired T-test: p=0.021 Table 3). Furthermore, there was a strong positive correlation between the first samples and the stored samples (R^2 = 0.98 figure 1)

Supplementary Table S3 shows the statistical tests for the 17 capillary samples that were immediately tested upon sample collection for HbA1c and then tested again after being stored at an average of 29.7˚C±0.69˚ C for 24 hours.

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	HbA1c pre30c storage (mmol/mol) - HbA1c post30c storage (mmol/mol)	1.23529	1.98524	.48149	.21458	2.25601	2.566	16	.021



Supplementary Figure 1 Pearson correlation co-efficient for both sample sets of blood for the 17 capillary samples stored at an average of 29.7˚C±0.69˚ C for 24 hours. Initial HbA1c pre30c storage on X-axis indicates samples taken on day of collection and HbA1c post 30c on Y-axis indicates retest after storage at 29.7˚C±0.69˚ C for 24 hours