Response to letter to editor: ‘Comment on Arch et al., Trials. 2016;17:517’

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Abstract: In October 2015 we published the paper ‘Measurement of HbA1c in multicentre diabetes trials – should blood samples be tested locally or sent to a central laboratory: an agreement analysis’. Chatterjee and Pradhan have submitted a letter to the editor asking critical questions regarding the methods we used. We offer this letter in response.

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Main text

We thank Chatterjee and Pradhan for their letter regarding our paper in Trials. 2016; 17-517. We agree with their sentiment that local HbA1c measurement cannot be implemented at the expense of clinically unacceptable disparities between centralised and localised measurements despite its greater cost efficiency. We hope that the following provides the additional information that will aid their assessment of our results.

Time-lag

In their letter, Chatterjee and Pradhan draw attention to Fig. 3 of our paper, and notice that within centres the distribution of differences is centred on 0 (suggesting that there are no centre-specific systematic biases present). We would argue that this does not imply that the same relationship would necessarily be true for time-lag. Figure 3 displayed results by site; however, within a site the time lag may vary. We have produced boxplots to show the distribution of differences by time-lag and a scatterplot as requested. This demonstrates an absence of a linear relationship between time-lag and discrepancy. They also indicate that in practice time-lag can be an important factor for high glucose values. As part of the underlying assumptions of the Bland-Altman method we investigated heteroscedasticity (see the Verification of assumptions section within the ‘Results’ section of our paper), i.e. we did not observe any increase in discrepancy with higher glycosylated haemoglobin (HbA1c).

Of the 590 measurements analysed for agreement, for 79 (13.4%) the date of measurement at the central laboratory was not recorded. These 79 are indicated with ‘M’ on Fig. 1 and excluded from Fig. 2 (scatterplot). For the remaining 511, in only 8 (1.5%) measurements was there a time-lag of more than 7 days. The Pearson’s correlation between time-lag and difference in measurements (local minus central HbA1c) was found to be −0.02. This was statistically not different from 0 (p = 0.48). This means that there is no evidence of a straight-line relationship (linear correlation) between time-lag and agreement. (See Figs. 1 and 2)

HbA1c measurement methodology

We specify in our paper that in almost all cases, both local and central, HbA1c was measured via immunoassay using portable machines. Local measurements were normally taken at outpatient clinics – but the technical method of measurement employed was not
recorded. At the time of analysis, we contacted all sites to establish what the local methodology was. Table 1 gives details of what the sites’ responses were.

We can give further detail here to say that the same portable machine was used at Alder Hey for outpatient clinics as at the central laboratory (based at Alder Hey). At this centre therefore, the methodology was identical. Differences were still incurred despite using the same machine with a short time-lag and removing the courier and post-transfer issues (see Fig. 3).

Whether central laboratory results should be used in preference to local results is an issue that needs to be considered at the design stage of any study. We hope that the information presented will enable greater clarity

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**Fig. 1** Boxplots showing the distribution of differences between local and central measurements by time-lag in days: between blood samples being taken and analysis at the central laboratory. M: measurements where the date of laboratory measurement was not recorded

**Fig. 2** Scatterplot showing the distribution of the magnitude of differences between local and central measurements by time-lag in days: between blood samples being taken and analysis at the central laboratory.
in decisions made. However, any decision needs to be born against the size of the effect that is to be detected and the potential size of discrepancies. This study demonstrates that despite quality control placed on local machines such discrepancies do occur. It should also be emphasised that this study took place in the UK and the climate and transport conditions elsewhere may determine whether local measurements are preferable.

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Availability of data and materials
The data for these analyses are available on request from the lead author.

Authors' contributions
All authors read and approved the final manuscript. BA carried out the analysis and wrote the statistical methods, results and much of the discussion section, and drafted the manuscript. JB wrote part of the background section and reviewed the manuscript. AM helped with data issues and reviewed the manuscript. JWG reviewed the manuscript. PN contributed the biochemistry methodology and reviewed the manuscript. CG raised the original question and led the statistical team contributing to the statistical analysis plan, analyses, and manuscript.

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1SCIPI: Randomised controlled trial of continuous subcutaneous insulin infusion compared to multiple daily injection regimens in children and young people at diagnosis of type I diabetes mellitus.

2CTRC: Clinical Trials Research Centre, University of Liverpool.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Table 1 Local HbA1c measurement methodology, as reported by sites

| Centre Code | Local measurement methodology |
|-------------|-------------------------------|
| 1           | Main method: DCA machine; 2 other possibilities: local laboratory or Hh9210 premier analyser machine by Menarini Diagnostics |
| 2           | Machine in clinic              |
| 3           | Diabetes team have their own machine |
| 4           | Method during follow-up: DCA machine in clinic calibrated daily with local laboratory |
| 5           | Machine on the ward            |
| 6           | DCA Vantage in the Diabetes Centre. QC managed by pathology department in the hospital |
| 7           | Siemens DCA Vantage machine in clinic |
| 8           | Alfiniton machine in outpatients |
| 9           | Portable DCA machine           |
| 10          | Machine in clinic              |
| 11          | Method during follow-up: DCA 2000 machine in clinic |
| 12          | Machine in clinic              |
| 13          | Main method: local laboratory (till April 2015); then new analyser machine |
| 14          | Technician from local laboratory brings a machine to the clinic |
| 15          | DCA analyser for majority of follow-up appointments |

QC quality control

Fig. 3 Scatterplot of discrepancies in measurements by time-lag at Alder Hey Hospital (location of central laboratory)
Ethics approval and consent to participate
SCIPI was approved by the accredited National Research Ethics Committee North-West – Liverpool East – on 31 March 2011 (Ref 10/H1002/80). The study protocol follows the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO), and it is compliant to ICH-GCP. All participants gave informed consent prior to enrolment in the study.

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