Choosing the duration of continuous glucose monitoring for reliable assessment of time in range: A new analytical approach to overcome the limitations of correlation-based methods

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Abstract

Aims: Reliable estimation of the time spent in different glycaemic ranges (time-in-ranges) requires sufficiently long continuous glucose monitoring. In a 2019 paper (Battelino et al., Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care. 2019;42:1593-1603), an international panel of experts suggested using a correlation-based approach to obtain the minimum number of days for reliable time-in-ranges estimates. More recently (in Camerlingo et al., Design of clinical trials to assess diabetes treatment: minimum duration of continuous glucose monitoring data to estimate time-in-ranges with the desired precision. Diabetes Obes Metab. 2021;23:2446-2454) we presented a mathematical equation linking the number of monitoring days to the uncertainty around time-in-ranges estimates. In this work, we compare these two approaches, mainly focusing on time spent in (70-180) mg/dL range (TIR).

Methods: The first 100 and 150 days of data were extracted from study A (148 subjects, ~180 days), and the first 100, 150, 200, 250 and 300 days of data from study B (45 subjects, ~365 days). For each of these data windows, the minimum monitoring duration was computed using correlation-based and equation-based approaches. The suggestions were compared for the windows of different durations extracted from the same study, and for the windows of equal duration extracted from different studies.

Results: When changing the dataset duration, the correlation-based approach produces inconsistent results, ranging from 23 to 64 days, for TIR. The equation-based approach was found to be robust versus this issue, as it is affected only by the characteristics of the population being monitored. Indeed, to grant a confidence interval of 5% around TIR, it suggests 18 days for windows from study
1 INTRODUCTION

In the last decade, the use of standardized continuous glucose monitoring (CGM)-based metrics to streamline data interpretation and to provide actionable information was largely recommended in several consensus panels.\(^1\)\(^-\)\(^4\) In particular, the use of the so-called ‘time-in-ranges’ (TIRs), that is, the percentage of time spent within different glycaemic ranges, was suggested by an international consensus panel convened by the Advanced Technologies & Treatments for Diabetes (ATTD).\(^4\) The same consensus panel recommended a minimum of 14 days of CGM to reliably estimate TIR. This recommendation was based on the results of analyses performed on data from randomized controlled trials,\(^5\)\(^,\)\(^6\) which assessed the correlation between TIRs computed over 3 months of CGM data and TIRs calculated in shorter periods of increasing durations. Specifically,\(^5\) showed that TIRs (and other glucose metrics) estimated over 12–15 days of CGM monitoring correlate well with the same metrics computed over the whole 3-month trial, using old generation sensors. The same result was obtained later,\(^6\) using the Abbott FreeStyle Libre Pro (Abbott Diabetes Care, Inc.) and the Dexcom G4 Platinum (Dexcom, Inc.) CGM systems.

This correlation-based approach was also used in several other works.\(^7\)\(^-\)\(^9\) In particular, Leelarathna et al.\(^7\) used 3-month hybrid closed-loop data and suggested a similar monitoring period as optimal. A longer optimal monitoring period of 4 weeks was suggested in a paediatric study,\(^8\) which analysed a longer dataset of 4-month duration. Finally, data with an even longer duration of 8 months were analysed using Abbott FreeStyle Libre and Dexcom G6 data, suggesting a minimum monitoring period of 5–9 weeks.\(^9\)

Apparently, the results of the correlation-based analysis seem to be strongly dependent on the total duration of the dataset employed. As recently noticed by Herrero et al.,\(^1\)\(^0\) this represents a limitation for the generalizability of the approach. Furthermore, the correlation-based approach does not provide a measure of the precision of the TIRs estimated over the suggested monitoring duration.

Conclusions: The equation-based approach offers advantages for the design of clinical trials having time-in-ranges as final end points, with focus on trial duration.

KEYWORDS
continuous glucose monitoring, correlation, estimation error, time-in-ranges, trial design

What is new?

• Numerous published papers focus on the identification of the minimum duration of CGM recordings in a clinical trial to reliably estimate time-in-ranges, by implementing a correlation-based approach.
• While the correlation-based approach is empirical and provides inconsistent results, we recently proposed a more robust analytical approach that suggests the minimum CGM duration to achieve the desired precision in time-in-ranges estimates.
• 3-weeks of CGM grant confidence-intervals of 5% around TIR and TAR, and 1.5% around TBR. Nevertheless, on https://computecgmduration.dei.unipd.it one can compute the adequate number of days needed to the purpose.
in [70–180] mg/dl ([3.9–10] mmol/L). Then, we implement the two approaches using two independent datasets, and evaluate the reliability of the minimum CGM duration identified. Specifically, for each approach, we assess whether the monitoring durations suggested are consistent to each other when changing the dataset used for the analysis.

2 | METHODS

2.1 | Datasets

We considered the datasets collected in two different studies.

Study A\textsuperscript{13} involves 148 participants (71 women) with T1D monitored for up to 6 months, using an unblinded CGM sensor without confirmatory fingerstick. The sensor used is a Dexcom G4 Platinum (Dexcom, Inc.) with enhanced accuracy through Software 505,\textsuperscript{14} providing one sample every 5 min. On mean ± standard deviation (SD), participants were 44 ± 14 years old, with HbA\textsubscript{1c} of 54 ± 7 mmol/mol (7.1 ± 0.7%), mean glucose of 161.6 ± 23.9 mg/dl, TIR of 61.8 ± 13.0%, time below range (TBR) of 3.92 ± 2.75%, time above range (TAR) of 33.1 ± 13.9% and coefficient of variation (CV) of 37.0 ± 5.05%. The available hours of CGM data were 3831 ± 598 h per person (data availability of 92.17%).

Study B is an observational study involving 45 participants (16 women) with T1D monitored for up to 1 year, conducted at the Medical University of Graz (IRB approval number: 29/522 ex 16/17). In this case, the CGM sensor used is Abbott Freestyle Libre, Abbott Laboratories, providing one sample every 15 min. On mean ± SD, participants were 39 ± 14 years old, with HbA\textsubscript{1c} of 60 ± 13 mmol/mol (7.7 ± 1.2%), mean glucose of 172.8 ± 34.1 mg/dl, TIR of 54.0 ± 17.7%, TBR of 5.15 ± 4.32%, TAR of 41.8 ± 19.3% and CV of 48.6 ± 6.69%. The available hours of CGM data were 7973 ± 689 h per person (data availability of 90.85%).

To ensure that an adequate amount of CGM data is available for each participant, only participants with at least 173 days of monitoring are retained for study A (90.67%) and only participants with least 330 days are retained for study B (88.89%), resulting in the exclusion of about the 10% of all the participants.

2.2 | Correlation-based approach

The correlation-based method can be illustrated as follows. Suppose that participants are monitored in a long-term trial lasting $N$ days (e.g. $N > 90$ days). For each participant $p = 1, 2, \ldots, N_{\text{par}}$, the most accurate estimate of the TIR, $\text{TIR}(p, N)$, can be evaluated over the whole trial duration $N$. The optimal trial duration $n_{\text{opt}}$ is defined as the minimum number of days needed to accurately reflect $\text{TIR}(p, N)$. To determine this value, several windows of increasing duration $n$, ranging in $[1, N]$ days, are extracted, simulating short-term trials. Then, $\text{TIR}(p, N)$ is computed for each of them.

Repeating this procedure for all the $N_{\text{par}}$ participants, the association between long-term TIR in the population, $\text{TIR}(N)$, and short-term TIR in the same population, $\text{TIR}(n)$, is assessed by resorting to the Pearson’s correlation coefficient $\rho$:

\[
\rho(n, N) = \frac{\sum_{p=1}^{N_{\text{par}}} (\text{TIR}(p, n) - \text{mean}(\text{TIR}(p, n))) (\text{TIR}(p, N) - \text{mean}(\text{TIR}(p, n)))}{\sqrt{\sum_{p=1}^{N_{\text{par}}} (\text{TIR}(p, n) - \text{mean}(\text{TIR}(p, n)))^2} \sqrt{\sum_{p=1}^{N_{\text{par}}} (\text{TIR}(p, N) - \text{mean}(\text{TIR}(p, n)))^2}}
\]

$n = 1, 2, \ldots, N$ (1)

The correlation coefficient $\rho(n, N)$ assumes values in $[0, 1]$ and it is expected to increase as the duration $n$ increases, reaching the maximum value of 1 when $n = N$.

Note that Spearman’s correlation coefficient can be used for variables which are not normally distributed, as suggested in Ref. [7]. Moreover, $\rho^2$ (also known as coefficient of determination) can be used instead of $\rho$. The key message of this paper remains valid also when considering these two alternative quantities to assess the correlation.

Once computed $\rho(n, N)$ for $n = 1, 2, \ldots, N$ days, the optimal CGM duration $n_{\text{opt}}$ to assess long-term TIR is selected as the number of days providing a desired value of correlation coefficient $\rho$ (or coefficient of determination $\rho^2$). For example, in Ref. [7] $\rho(n, N) = 0.95$ was considered, while in Ref. [9] the optimal duration $n_{\text{opt}}$ was selected as the one providing $\rho^2(n, N) = 0.9$.

2.3 | Equation-based approach

The analytical approach of Camerlingo et al.\textsuperscript{11} can be briefly illustrated as follows. In the same framework previously described, the estimation error committed using short-term TIR, $\text{TIR}(p, n)$, instead of the more accurate $\text{TIR}(p, N)$ is computed for each participant $p = 1, 2, \ldots, N_{\text{par}}$, as follows:
This quantity can be both positive and negative and it is distributed around 0 with a certain SD SD[e(n)]. The larger this quantity, the more uncertain the estimate TIR(p, n).

We previously derived and validated an equation to calculate the SD of the estimation error SD[e(n)] as a function of the length of the monitoring period n:\(^\text{11}\):

\[
\text{SD}[e(n)] = \sqrt{\frac{P_t (1 - P_t)}{kn} \left( 1 + \frac{2\alpha}{1 - \alpha} + \frac{2\alpha}{kn} \frac{(a^k n - 1)}{(1 - \alpha)^2} \right)}
\]

(2)

This equation proved effective in predicting the uncertainty of several TIRs estimates, computed retrospectively by CGM data collected in two large populations of T1D individuals, using different sensors.\(^\text{12}\)

Equation (2) involves three parameters: \(k, p_t\) and \(\alpha\). The first parameter, \(k\), depends only on the sensor sampling period, that is, how often the sensor provides a measurement (usually every 5 or 15 min). Specifically, \(k\) amounts to the number of CGM samples produced in 1 day when no data gaps occur. For example, \(k = 288\) for a CGM sensor providing measurements every 5 min, while \(k = 96\) for CGM measurements collected every 15 min.

The second parameter, \(p_t\), depends on the considered glycaemic range and on the population under study. In particular, it represents the average TIRs in the population. This value is unknown when designing a new study, thus a clinical practitioner should be set it to the expected TIRs in the population under analysis, based on pilot study, clinical experience of previously reported data or educated guess (analogously to power calculation tools, that requires setting a priori the expected effect size).\(^\text{15}\)

The third parameter, \(\alpha\), is poorly sensitive to the population under analysis, while it depends the most on the considered glycaemic range and the CGM sensor sampling period. Moreover, small errors in setting the value of \(\alpha\) impact very slightly on the predicted uncertainty.\(^\text{16}\)

Hence, in Ref. [12] some plausible TIRs-specific values of \(\alpha\) were suggested: using a CGM sensor providing one measurement every 5 min, \(\alpha_5 = 0.961\) for the TIR, \(\alpha_5 = 0.940\) for the TBR and \(\alpha_5 = 0.968\) for the TAR. Then, according to the rule provided in Ref. [12], these values can be adapted for sensors with different sampling periods: in general, when a sensor providing one measurement every \(T\) minutes is used, the previous values should be adjusted accordingly as \(\alpha_T = \alpha_5^{\frac{T}{5}}\).

Given the above considerations, for the TIR and a 5-min CGM sensor Equation (2) becomes:

\[
\text{SD}[e_{\text{TIR}}(n)] \approx \frac{P_t (1 - P_t)}{96 n} \left( 18.05 - \frac{1.691}{n} \right)
\]

(3)

Finally, once obtained the explicit formula, the optimal CGM duration \(n_{\text{opt}}\) is determined as the number of days \(n\) granting a desired level of uncertainty around the TIR estimate, \(\text{SD}[e_{\text{TIR}}(n)]\). To facilitate this computation, an online calculator was developed and made freely available at: http://computevgmduration.dei.unipd.it.

### 2.4 Comparison of the two approaches

To compare the two approaches, we investigated how the minimum monitoring duration, suggested by each method, changes:

1. When the length \(N\) of the trial used for the analysis changes, but both the populations of participants under study and the CGM sensor used remain unchanged;
2. When the length of the trials used remain the same but the population of participants under study and the CGM sensor used change.

These two analyses are relevant since one would like to get from the methods a minimum duration that is independent on the trial duration used to determine it. On the contrary, it is reasonable that different populations might require a different minimum monitoring time based on their inherent characteristics.

To investigate the first question, we selected portions of increasing duration from study B (the longer of the two under analysis) all starting from the first day, thus simulating trials with different durations \(N\), conducted on the same participants with the same sensors. Specifically, we obtained the trials B1, B2, B3, B4 and B5 lasting 100, 150, 200, 250 and 300 days respectively. Then, we compared the results obtained by the correlation-based and the equation-based approaches.

To investigate the second question, we extracted the first 100 and 150 days from study A, thus obtaining the trials A1 and A2, and compared the results obtained by applying the correlation-based and the equation-based approaches for A1 versus B1 and A2 versus B2.

In the implementation of the correlation-based approach, the coefficient of determination \(\rho^2(n, N)\) was computed, retrospectively, by CGM data of each trial. Then, the optimal CGM duration was selected as the minimum number of days \(n_{\text{opt}}\) providing \(\rho^2(n, N) = 0.9\), as in Ref. [9] To obtain a stable value of \(\rho^2(n, N)\), we employed a sliding window approach.\(^\text{10}\) Further notes in this regard
are reported in the Supplementary Material (see, for example, Figure S1).

In the implementation of the equation-based approach, we used the online tool available at http://computecgm.dur.ualberta.ca, setting the parameters as follows. The sensor sampling period was set to 5 min for study A and to 15 min for study B; the parameter \( p_{r} \) was computed, for each trial, as the mean TIR in the population; the desired uncertainty \( \text{SD}[e(n)] \) was set to 5%. So, the optimal CGM duration was selected as the minimum number of days \( n_{\text{opt}} \) providing \( \text{SD}[e(n)] = 0.05 \).

Note that the threshold values of 0.9 for \( p^{2} \) and 0.05 for \( \text{SD}[e(n)] \) do not have a specific clinical meaning, and are not linked between each other (i.e. having a \( p^{2} \) equal to 0.9 is not equivalent to have a \( \text{SD}[e(n)] \) of 5% and there is not a straightforward way to define such an equivalence). Therefore, we cannot directly compare the results obtained by the two approaches on the same trial, but we can analyse how the results obtained by each approach vary for different trials.

For a more comprehensive assessment, independent of the threshold value, we also analysed the pattern of \( p^{2}(n,N) \) as a function of \( n \), for the correlation-based approach, and the pattern of \( \text{SD}[e(n)] \) as a function of \( n \), for the equation-based approach, considering initial trials of different durations \( N \) (B1, B2, B3, B4 and B5).

3 | RESULTS

Table 1 reports the optimal number of monitoring days, \( n_{\text{opt}} \), provided by the correlation-based approach with target \( p^{2} \) equal to 0.9 (column 5) and the equation-based approach with desired \( \text{SD}[e(n)] \) of 5% (column 6), for the trials A1, A2, B1, B2, B3, B4 and B5. For each trial, the whole trial duration \( N \) is reported (column 3), as well as the TIR computed on the overall trial (column 4), expressed as mean ± SD.

First, let us compare the results obtained for the trials of different durations extracted from study B.

The equation-based approach returns a unique optimal trial duration of 18 days for all the trials extracted from study B. Indeed, the trial duration \( N \), not present in Equation (3), does not affect the result of this approach. Conversely, the correlation-based approach yields different results for each trial. In particular, the longer the trial the more days are needed to reach the desired \( p^{2} \): for B1, whose duration is 100 days, the optimal trial duration is 23 days, while it reaches 64 days for B5, which lasts 300 days. This shows that the minimum monitoring time suggested by the correlation-based approach is influenced by the duration of the trial used for the analysis. Notably, this happens even if the TIR values for B1, B2, B3, B4 and B5 are very similar to each other, thus reasonably allowing to exclude that the correlation approach is offering different suggestions because the population is changing during the study.

To generalize these considerations to different \( p^{2} \) and \( \text{SD}[e(n)] \) target values, in Figure 1 we report the curves of \( p^{2}(n,N) \) versus \( n \) obtained with the correlation-based approach (Figure 1a) and the curves of \( \text{SD}[e(n)] \) versus \( n \) obtained with the equation-based approach (Figure 1b), for trials of different duration \( N \): B1 (circle green), B2 (triangle cyan), B3 (square blue), B4 (diamond red) and B5 (asterisk black). On one hand, the \( p^{2}(n,N) \) curves are shifted for different trials: the lower the trial duration \( N \), the faster they increase. Thus, for any \( p^{2} \) threshold, the minimum number of days returned by this approach varies with the overall trial duration \( N \). For example, it is smaller for B1 (\( N = 100 \) days) than for B5 (\( N = 300 \) days). On the other hand, the \( \text{SD}[e(n)] \) curves showed in panel b for different trials are perfectly overlapped, since the

| Study | Trial | Trial duration \( N \) [days] | TIR (N) [mean ± SD] | Optimal trial duration \( n_{\text{opt}} \) [days] |
|-------|-------|-------------------------------|---------------------|----------------------------------|
|       |       |                               |                     | Correlation based | Equation based |
| B     | B1    | 100                           | 55.8 ± 15.3%        | 23                  | 18 |
| B     | B2    | 150                           | 55.1 ± 14.9%        | 27                  | 18 |
| B     | B3    | 200                           | 54.8 ± 14.4%        | 35                  | 18 |
| B     | B4    | 250                           | 54.9 ± 14.0%        | 46                  | 18 |
| B     | B5    | 300                           | 54.7 ± 13.7%        | 64                  | 18 |
| A     | A1    | 100                           | 62.0 ± 13.5%        | 24                  | 17 |
| A     | A2    | 150                           | 62.3 ± 13.3%        | 28                  | 17 |

Note: The \( p^{2} \) target for the correlation-based approach is 0.9, while the \( \text{SD}[e(n)] \) target for the equation-based approach is 5.0%. Abbreviations: SD, standard deviation; TIR, time-in-range.
overall trial duration $N$ does not affect the results of the equation-based approach and the $p_r$ values are quite similar among the trials.

In Table 1 we can also compare the results obtained for the trials of equal durations $N$ extracted from different studies, in particular trials A1, B1 of duration $N = 100$ days, and trials A2, B2 of duration $N = 150$ days.

The equation-based approach suggests that the minimum CGM duration to reflect TIR of both trials A1 and A2 is 17 days, that is, slightly lower than the one obtained for the trials extracted from study B (18 days). Such small difference is due to the different TIR values for the populations of study A and study B (nearly 10% difference in TIR), which are taken into account by the parameter $p_r$. This means that the results of the equation-based approach may be different for different populations, but, as previously noticed before, they are not sensitive to the overall trial duration. Also considering the correlation-based approach, the different characteristics of the population slightly impact on the results (e.g. the minimum CGM duration estimated for trial A1 is 24 days vs. 23 days for trial B1). Nevertheless, the results of the correlation-based approach are significantly affected by the trial duration: for trials lasting 150 days (A2 and B2) the minimum CGM duration obtained is 4 days higher than that obtained for trials lasting 100 days (A1 and B1).

In summary, the correlation-based approach results more sensitive to the trial duration $N$ than to the characteristics of the population under study. Conversely, the equation-based approach is by design independent on the trial duration $N$, although it can be influenced by the population characteristics, which are summarized by parameter $p_r$, representing the population average long-term TIR.

As a further note, interestingly, expressing the results obtained by the correlation-based approach in terms of fraction of the trial duration $n/N$, they are all around the
TABLE 2 Optimal trial duration obtained with the correlation-based approach and the equation-based approach, considering TBR, for trials extracted by study A (A1 and A2) and study B (B1, B2, B3, B4 and B5)

| Study | Trial | Trial duration N [days] | TBR (N) [mean ± SD] | Optimal trial duration n_{opt}[days] |
|-------|-------|-------------------------|---------------------|------------------------------------|
| B     | B1    | 100                     | 4.74 ± 4.47%        | 35                                 |
| B     | B2    | 150                     | 4.77 ± 4.21%        | 43                                 |
| B     | B3    | 200                     | 4.98 ± 4.31%        | 60                                 |
| B     | B4    | 250                     | 5.21 ± 4.43%        | 72                                 |
| B     | B5    | 300                     | 5.20 ± 4.34%        | 84                                 |
| A     | A1    | 100                     | 3.61 ± 2.60%        | 36                                 |
| A     | A2    | 150                     | 3.64 ± 2.57%        | 45                                 |

Note: The $r^2$ target for the correlation-based approach is 0.9, while the SD[ε (n)] target for the equation-based approach is 2.0%

Abbreviations: SD, standard deviation; TBR, time below range.

20% (23.0% for B1, 18.0% for B2, 17.5% for B3, 18.4% for B4, 21.6% for B5, 24.0% for A1 and 18.6% for A2). This result suggests that the correlation-based approach identifies only the fraction of the trial duration, $n/N$, needed to match the long-term TIR. This consideration remains valid also with different $r^2$ thresholds, as shown in Figure 2, where $r^2(n, N)$ is reported against the fraction of trial duration $n/N$, for the trials A1 (triangle yellow), A2 (star purple), B1 (circle green), B2 (triangle cyan), B3 (square blue), B4 (diamond red) and B5 (asterisk black). All the curves are almost overlapped, driving to the conclusion that, for any $r^2$ threshold values, the optimal trial duration returned by the correlation-based approach is a fixed fraction of the trial duration, whose specific value depends on the $r^2$ threshold. For example, for $r^2 = 0.9$, the method returns a number of days that is about 20% of the total trial duration ($n/N = 20%$), while for a $r^2$ threshold of 0.95 the method returns a number of days that is about 40% of the total trial duration ($n/N = 40%$).

4 | DISCUSSION

Setting a suitable duration of a clinical trial is fundamental to grant the reliability of the experimental findings. In this work, we focused on trials having TIRs as final end points and compared two approaches to determine the minimum CGM duration to precisely estimate TIR. The first approach, commonly employed in the literature, assesses the correlation between the TIRs computed over a whole dataset and the TIRs computed over shorter periods of increasing durations. The optimal number of days provided as a result by this approach can be read as the minimum monitoring period required to achieve TIR values strongly correlated with those computed over a long-term dataset. The second approach, recently proposed by our group, relies on a mathematical equation linking the trial duration to the precision of a TIR estimate, by means of three parameters. Among them, only the parameter $p_t$, that is, the expected TIRs of the population being analysed, should be set based on pilot studies, educated guess, clinical experience of previously reported data. The optimal number of days provided as a result by this approach represents the minimum monitoring period required to achieve a desirable precision in the final TIRs estimates. While in Ref. [11] we illustrated the mathematical formulation of the problem, and in Ref. [12] we validated the resulting mathematical equation over different TIRs, different populations of participants with heterogeneous characteristics and different CGM sampling periods, in this work we compared the new analytical approach against the correlation-based approach by assessing whether their results are consistent to each other when changing the dataset used for the analysis. Specifically, we considered portions of data of different duration extracted from the same study and datasets of equal duration extracted from different studies. The analysis showed that the correlation-based approach yields different results for different trial durations: the longer the dataset employed, the longer the suggested minimum duration. On the contrary, the minimum duration indicated by the analytical approach is, by design, independent on the duration of the dataset used, and reflects the TIRs of the population being analysed. In this regard, we recently demonstrated\textsuperscript{16} that plausible errors in guessing the TIRs in the population to be monitored (up to ±13% for TIR) slightly impact on the results of the proposed mathematical formula and, thus, do not tamper the applicability of the analytical approach.

REPLACE-BG dataset (referred herein to as study A)\textsuperscript{13} was used in this paper to illustrate with a retrospective example the comparison of the two approaches, because of the large number of participants, but it should be acknowledged that it includes only participants without significant hypoglycaemia unawareness and with low risk of
developing severe hypoglycaemia. Instead, the second dataset considered in this work (referred to as study B) included participants with a higher exposure to hypoglycaemia (TBR of study B is around 40% greater than in study A).

For illustration purposes, we focused on TIR only and showed that the correlation approach provides different results when applied to datasets with different lengths, while the analytical approach offers consistent suggestions. This message holds also for other TIR indices as well, for example, the fraction of time spent with CGM <70 mg/dl (TBR) and the fraction of time spent with CGM >180 mg/dl (TAR) as shown in Tables 2 and 3 for a target uncertainty of ±2% in TBR and ±5% in TAR. Nonetheless, the optimal duration of CGM data depends on the TIR index considered as outcome metric, with markedly long durations of CGM data needed to precisely estimate TBR, compared to TIR and TAR, as pointed out in several works.7,10,12 This is also predicted by the proposed analytical approach, as illustrated in Figure S2 that shows how TIR, TBR and TAR relative uncertainties decrease as the trial duration increases.

According to the analyses presented in this work, it could be worth extending the minimum monitoring duration from 2 weeks (as suggested by the current ATTD consensus)13 to 3 weeks, that would grant about 5% confidence interval around TIR and TAR estimates, and about 1.5% confidence interval around TBR estimates. Moreover, if other levels of accuracy are deemed necessary to draw solid scientific conclusions, the analytical approach can be used to compute an adequate number of days for the purpose. In this regard, the use of the analytical approach is analogous to power calculation tools, allowing computing the number of subjects to be recruited in a trial based on the desired power and population-specific quantities.

The analytical approach may be used in clinical practice both to assess the precision of TIRs obtained in published studies, and in future studies, in combination with standard power calculation tools, to optimize the cost-benefit ratio of a clinical trial. While nowadays the correlation-based approach suggests a standard CGM duration of 14 days to evaluate TIR, the analytical approach can provide the confidence interval (i.e. the precision) around the final estimate, for any monitoring duration: the longer the study, the tighter the confidence interval (i.e. the more precise the estimate). Diabetologists would benefit of this approach (by means of the free user-friendly online calculator) to determine the minimum number of days needed to draw solid scientific conclusions, based on the purpose of the trial.

In conclusion, the correlation-based approach provides results that are sensitive to the original trial duration, and as such, they cannot be generalized for the planning of trials of different duration. For this reason, the equation-based approach offers advantages for the design of clinical trials having TIRs as final end points.

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**CONFLICT OF INTEREST**

PC has received personal fees from Medtronic, Abbott, Dexcom, Insulet, Novo Nordisk, Lilly and Sanofi. JKM is a founder of the decide Clinical Software Ltd. JKM is a member in the advisory board of Abbott Diabetes Care, Becton-Dickinson, Boehringer Ingelheim, Eli Lilly, Medtronic, NovoNordisk A/S, Prediktor A/S, Roche Diabetes Care, Sanofi-Aventis and received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Becton-Dickinson,

| Study | Trial | Trial duration N [days] | TAR (N) [mean ± SD] | Optimal trial duration n_{opt} [days] |
|-------|-------|-------------------------|---------------------|-------------------------------------|
| B     | B1    | 100                     | 41.6 ± 17.7%        | Correlation based: 21; Equation based: 21 |
| B     | B2    | 150                     | 41.8 ± 18.7%        | Correlation based: 28; Equation based: 21 |
| B     | B3    | 200                     | 41.4 ± 18.8%        | Correlation based: 35; Equation based: 21 |
| B     | B4    | 250                     | 41.3 ± 18.7%        | Correlation based: 44; Equation based: 21 |
| B     | B5    | 300                     | 41.4 ± 18.4%        | Correlation based: 58; Equation based: 21 |
| A     | A1    | 100                     | 31.2 ± 13.1%        | Correlation based: 27; Equation based: 19 |
| A     | A2    | 150                     | 30.9 ± 12.8%        | Correlation based: 30; Equation based: 19 |

Note: The r² target for the correlation-based approach is 0.9, while the SD{e (n)} target for the equation-based approach is 5.0%

Abbreviations: SD, standard deviation; TAR, time above range.
Dexcom, Eli Lilly, NovoNordisk A/S, Roche Diabetes Care, Servier and Takeda. The other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
Nunzio Camerlingo and Simone Del Favero contributed to the design of the research and drafted the manuscript. Pratik Choudhary, Martina Vettoretti, Andrea Facchinetti, Giovanni Sparacino and Julia K. Mader contributed to the interpretation of the results. Julia K. Mader provided part of the data. The final version was read, reviewed and approved by all authors.

DATA AVAILABILITY STATEMENT
Data of study A can be obtained from the T1D Exchange archive (https://t1dexchange.org/research/biobank/). The online calculator is available at: http://computecgmduration.dei.unipd.it. All the code implementing the proposed methodology in Matlab are publicly available at: https://github.com/NunzioCamer/A/misc/AnalyticalTBRestimation.

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SUPPORTING INFORMATION
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