How to collect non-medical data in a pediatric trial: diaries and interviews

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Research

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Abstract

Background: Non-medical data such as patients' and caregivers' time can be relevant to assess therapeutic strategies. For chronic pediatric conditions, patients' and caregivers' time spent in seeking and providing care (i.e. indirect cost in an economic evaluation) can be significantly different depending on the treatment arm. In order to explore methods to collect information on care burden for caregivers and patients, we investigated whether or not a patient diary provided additional information compared to retrospective investigator-led interviews and whether a diary filled intermittently produced more or less information than a continuous diary. The main objective of this study was to identify which type of data collection was most effective to measure caregivers' time and estimate indirect treatment costs over a 9-month period. Methods: Start-In! is a randomized controlled trial comparing the efficacy of three strategies of real-time continuous glucose monitoring (CGM) for 12 months in children and adolescents with type 1 diabetes. We designed an ancillary study to assess methods of patients' and caregivers' time (indirect costs): data entered was retrospectively in the case report form by investigators during quarterly follow-up visits, with the help of diaries filled prospectively by children or caregivers either continuously or intermittently. Data about absence from school and work as well as caregivers' time for diabetes care were collected and comparisons carried out between the three collection methods. Results: At the end of the 9-month study, 42% of study participants failed to return their diary. For the diaries that were received, less than 10 were contributive on top of the information entered on 82 patients directly by investigators .Based upon this information, we calculated that over 9 months, caregivers lost on average 3.9 days of working time, (€786), and 4 days of personal time, i.e. the equivalent of €526, as well as around 15 minutes of care per day, i.e. the equivalent of €1,700. Conclusions: Data collection by investigators during quarterly visits cannot be replaced by a diary. The completion of diaries appeared to represent an important additional burden to children and their caregivers and provided limited additional information compared to investigators 'entries in the CRF. Trial registration: Start-In! trial registry name: Study of Insulin Therapy Augmented by Real Time Sensor IN Type 1 Children and Adolescents (START-IN!). ClinicalTrials.gov Identifier: NCT00949221. Registered on July 30, 2009.

Background

Non-medical data such as patients' and caregivers' time can be relevant to assess the full burden and cost of therapeutic strategies. The pertinence of including time costs for caregivers and patients as indirect costs in economic evaluations of therapeutic strategies is debated during the protocol writing and mainly depends upon the perspective of the evaluation and the type of illness considered (1). Productivity losses can represent a significant amount of resources in particular for chronic pediatric conditions when caregivers are involved to seek and also provide care for children. Information on absence from work or school is not collected in health insurance databases and needs to be estimated either with retrospective interviews by an investigator (2), or with diaries completed by the parents or patients (3,4). Investigator–led interviews require additional work from the physicians which could be reduced if children or caregivers completed diaries prospectively (5). However, using a paper or electronic diary in clinical trials

requires logistical management and fastidiousness from participants, especially for studies with long follow-up periods (6). The question seemed all the more important in pediatric trials where parental constraints may influence the acceptance of additional data collection (7).

In order to explore the best way to collect information on care burden and time costs, we investigated whether or not a patient-filled diary provided additional information compared to retrospective investigator-led interviews and whether a diary filled intermittently produced more or less information than a continuous diary. We hypothesized first that a diary would enable investigators to shorten their interviews, being helped or even replaced with diaries. We assumed that patients would have a tendency to under-report their time costs. Our second hypothesis was that keeping a continuous diary was an onerous task and could lead to fatigue and poor data collection over time. However, the intermittent diary, while reducing the data entry burden for patients (8), would carry the risk that patients may fail to complete the diary if it was not a regular task.

The main objective of this study was to identify which type of data collection was most effective for obtaining information on care burden and time costs over the 9-month period of a pediatric trial. The secondary objectives were to determine the patient acceptance for an intermittent versus a continuous diary and to look for a decreasing trend in the amount of data collected over time.

Methods

Study design

We designed an ancillary study to the Start-In! trial (NCT00949221) which compared the efficacy and cost-effectiveness of three strategies of real-time continuous glucose monitoring (RT -CGM) in type 1 diabetes children (T1D) (9). This trial was well adapted to our study objective since insulin–dependent diabetes in children is a chronic condition with major time costs to children and their parents.

Start-In! was a French multi-center trial with a randomized, controlled, prospective, open, parallel group design, comparing three therapeutic modalities in pediatric management (9).

Patients were aged from 2 to 17 years, diagnosed with T1D for more than one year, treated by intensive insulin therapy, with inadequate metabolic control. The study was conducted in 11 pediatric diabetology units with expertise in pump therapy and CGM. The primary endpoint was long term glycemic control at 12 months. The clinical study had two phases: all subjects wore the RT-CGM during the first three months, and thereafter were randomized in three groups with different strategies of glucose monitoring during the next 9 months. The ancillary study reported here concerns the 9-month patients' follow-up period (Figure 1.).

The Start-In! economic evaluation required information on consultations, absence from work /school due to diabetes and daily time spent by the caregiver to provide diabetes care. This information was entered

for all patients by the investigators in the paper case report form (CRF) at the end of each trimester and represented the reference strategy.

In order to test whether diaries would provide additional information, patients were randomized into two groups. In the ‘continuous diary’ group, children and caregivers were asked to collect data in a diary without interruption during one of the three trimesters of the study (three months continuously). In the ‘intermittent diary’ group, data was collected during the last month of each of the three trimesters only. Randomization was conducted following a 3:1: ratio. In the continuous diary group, the diary was filled daily for one of the three trimesters of the study follow-up period. The trimester was randomized with a 1:1:1 randomization. To simplify the work of investigators, the randomization for the ancillary study was by center and not by patient (Fig.2 and 3). Data from the patient interview and diaries were entered in the CRF by investigators following the same schedule: one trimester for the ‘continuous’ group and last month of each for the ‘intermittent’ group.

Endpoint

The primary endpoint was the amount of information measured by the number of absences from school and work recorded (as many dates as required could be entered), number of consultations and caregiver time for diabetes care, collected in the diaries, compared to the information given to the investigator during the quarterly follow-up visit.

Material

The Start-In! participants (patient, caregivers) were asked to record their absences from school and from work, the number and dates of the consultations in the diary and how many caregivers were present at the consultation with an estimate of the daily time spent by the caregivers to provide diabetes care such as blood glucose monitoring and insulin administration (see Additional file 1). There was no minimum or maximum limit on the number of absences or visits recorded. The same information was also collected quarterly by the investigator and entered in the CRF with the help of the diary that was collected at the same time.

Analysis

The number of absences from work or school and number of consultations were calculated from the data entered in the diaries for each patient. Regarding the daily time spent by the caregiver, only one variable was required for completion which was the average caregiver time spent in 24 hours. When this variable was not completed it was considered to be missing data rather than zero. Regarding the other variables (dates of absences from school, from work, and dates of consultations) when they were not filled we considered them missing data if the daily time spent by the caregiver was equally missing. The global amount of information calculated was compared between the groups ‘intermittent’ and ‘continuous’.

Similarly, the amount of information entered by the investigators into the CRF was calculated and compared to each diary group, either ‘continuous’ or ‘intermittent’.

Care burden and indirect costs

Regarding the calculation of indirect costs for the economic evaluation, the time spent by patients and their families was valued based on the average salary cost in France for those in employment (€34 per hour) and the average salary cost of a house cleaner for the unemployed (€18.7 per hour) as the opportunity cost. The average daily time spent by a caregiver administering diabetes care to the patient was valued by the cost/minute of a home nurse (€28.8 per hour). All costs are in Euros (€) 2017 (1€ = 1.2US$) and are not discounted due to the short time horizon.

Results

A total of 151 patients were first randomized in the Start-In! trial, 52 in Group 1, 48 in Group 2 and 51 in Group 3. Their characteristics were similar at inclusion (9) with an average age of 12 years and a nearly 50:50 ratio boys to girls, although there was quite a difference in age and sex between the centers as seen in Table 1. A total of 23 patients left the study were initially excluded from the our ancillary analysis of the diary data as their diaries would be obviously empty. Thus 128 patients were available for analysis of the diary data with 92 randomized in the 'continuous' group and 36 in the 'intermittent' group, while information on care burden was otherwise collected on all 151 patients by the investigators during the follow up visits.

Table 1: Frequency, mean age and boys/girls sex ratio of patients by centers at inclusion.

	Patients		
Centre	Frequency	Mean age (years)	Sex ratio (boys/girls)
1	30	11.1	1.14
2	31	11.2	2.88
3	17	11.8	1.43
4	9	12.3	0.80
5	19	13.9	0.36
6	13	10.9	0.44
7	9	14.2	0.50
8	8	11.7	1.67
9	6	9.8	0.50
10	6	11.5	2.00
11	3	12.5	0.50
All	151	11.8	1.04

Primary endpoint

Half of the 128 patients in this analysis did not return diaries so their information reported to the investigators and entered in the CRF was based solely on memory.

'Continuous diary' group

Of the 92 patients, only 53 % (n=49) returned a diary. Among the 49 returned diaries, 44 were empty and each type of data were then considered missing data, 4 reported that no absences occurred, and only one diary gave a date of absence from work/school. That is 99% of missing data among collected diaries, and 99.5% among all diaries from all patients.

'Intermittent diary' group

Of the 36 patients, just under half (n=16) returned at least one diary. Each patient should have submitted three diaries, one by trimester, but only 41 of the 108 diaries expected were collected. In those 41 diaries, missing data were 97.6%, as only one diary was filled. Among all diaries from all patients, missing data were 99%.

Investigator-filled CRF

The same information was collected retrospectively from the patients and caregivers by investigators who entered them in the CRF at the trimestral follow-up visit,. The information was obtained directly by the investigators from interviews, potentially supplemented by the data entered prospectively in the diaries.

Table 2 shows data completion of the CRF by the investigator for patients whose diaries were missing or empty, depending on their randomization group ('continuous' or 'intermittent'). In the 'continuous diary' group, regarding *Absences from work*, among the 87 patients having either returned an empty diary or no diary, 73 had information entered in their CRF about their absences from work. For the *Consultations* section, among the 35 patients from the 'intermittent diary' group with empty or no diaries, an average of 34 had information entered in the CRF.

The quantity of information from the CRF has enabled us to calculate a percentage of missing data in the same way we did for diaries. The 'continuous' group shows a tendency to have more missing data in the CRF filled by investigators than the 'intermittent' group (14% vs. 5%) which is far less than the around 99% of missing data in diaries.

Table 2: Frequency of CRF filled with empty or no diaries, depending on randomization and type of data among the patients.

	No. (%) of CRF with data on patients' and caregivers' burden	
Type of data filled in the CRF by the investigator	**Group 'continuous' with an empty diary N=87**	**Group 'intermittent' with an empty diary N=35**
Absences from school	78 (90)	34 (97)
Absences from work	73 (84)	32 (91)
Consultations	81 (93)	34 (97)
Time for diabetes care	68 (78)	33 (94)

Care burden and Indirect costs

Since the CRF, based upon interviews and diaries, collected about 80% of the indirect cost data, we calculated productivity losses and indirect costs. Over 9 months, parents lost on average 3.9 days of working time, i.e. the equivalent of €786, and 4 days of unemployed time, i.e. the equivalent of €526, as well as around 15 minutes of care per day, i.e. the equivalent of €1,700.

Children were absent from school an average of three days over 9 months.

Discussion

Some trials require the collection of non-medical data that are not readily available in patients' charts or claims database. Investigators have the options of relying on patients' memory at the time of follow-up visits, or to provide diaries. The objective of our data collection was to estimate indirect medical costs in each treatment arm and identify possible differences which would not be captured by the calculation of direct medical costs based upon information systematically retrieved from hospital claims data. All investigators had to enter in the CRF data on caregivers and patients burden (time) and relied on both interviews and diary information. Our study compared two prospective methods to document the treatment burden for caregivers and patients of T1D in children during a clinical trial including an economic evaluation. The major finding was the magnitude of missing data in the diaries provided to caregivers for completion (around 99%). While the average cost of caregivers' time could be estimated from investigator-led interviews to be around €3,000 per patient over 9 months, the information from diaries alone did not allow a reliable estimate. It would appear that diaries filled by families to collect non-medical information in a pediatric trial for a severe chronic condition are unsuitable and we do not recommend their use.

The amount of data entered by investigators for patients in the 'intermittent diary' group was slightly higher than the 'continuous' group (95% vs.86%). This tendency may be explained by the participants having to remember only one month of information at the time of an interview instead of three (10). In this trial, the CRF always contained more data than the diaries since it was based upon interviews by the investigators who could be helped by the diary contents (when the diaries were completed). In fact,

diaries can be a reliable source of data to complement usual reporting methods as shown by Dunn et al. (5) but we were not able to confirm this conclusion, because of the amount of missing diary data.

Many studies from different countries show a high concordance between self-reported and medical records of health care resource utilization in the general patient population (11,12). We were interested in the particular case of pediatric trials, where diaries would be filled by caregivers who are often tired from caring for a chronically ill child in addition to their jobs and may have other children to take care of. In fact, family members of someone with diabetes seems to be at higher risk of depression (13) and parents of a child with Tb1 not only struggle with depression (14,15) but also worry about hypoglycemia (16) which can lead to parental emotional distress (17). Difficulties are encountered with adolescent patients, who are becoming more independent but have troubled relationships with their parents (18) and transition issues like treatment adherence (19,20). In those circumstances, reporting non-medical data like school absences is not a priority for the family.
Unfortunately the patients and their caregivers were not asked their opinion about the different data collection, so we can only speculate about the cause of so much missing data. This study has other limitations. The amount of missing data prevented us from performing statistical tests or evaluating our secondary objectives of patient acceptance and fatigue effect. With such little data the quality of information could not be assessed and thus only the quantity was explored in our trial.

Conclusions

Trials that require non-medical data may need to rely on patients and families for information. In our study of a pediatric chronic condition, investigator-led interviews provided a lot more information than patient diaries. The completion of diaries appears to represent an important additional burden to children and their families who are already struggling with many competing issue. Notwithstanding, the large amount of indirect costs associated with the loss of parental productivity underlines the importance of collecting these data, in one way or another.

Declarations

Ethics approval and consent to participate

The AFSSAPS (National Agency for the Safety of Medicines and Health Products) approved the protocol of the START-IN! trial. Reference number: 2007-AO1330-53. Informed consent was obtained from all study participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Competing interest

The authors declare that they have no competing interests.

Authors' contribution

ALJ wrote the manuscript. ALJ and HM carried out the analysis. IDZ supervised the methodology and statistical analysis. ALC, IDZ, SGC, CA and NTR contributed to the methodology. All authors revised the manuscript.

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Additional File Legends

Additional file 1 (.pdf): Data collected by patients in the diary.ies and CRF.

This file presents all the data collected in the patients' diaries regarding indirect costs needed for the economic evaluation, for the last month: the dates of children's' absences to school/work, the dates of the parents' absences to work, the dates of medical consultations with the number of adults attending, and finally an estimation of the time spent at home during 24 hours by adults relatives for anything regarding diabetes treatment and care.

Figures

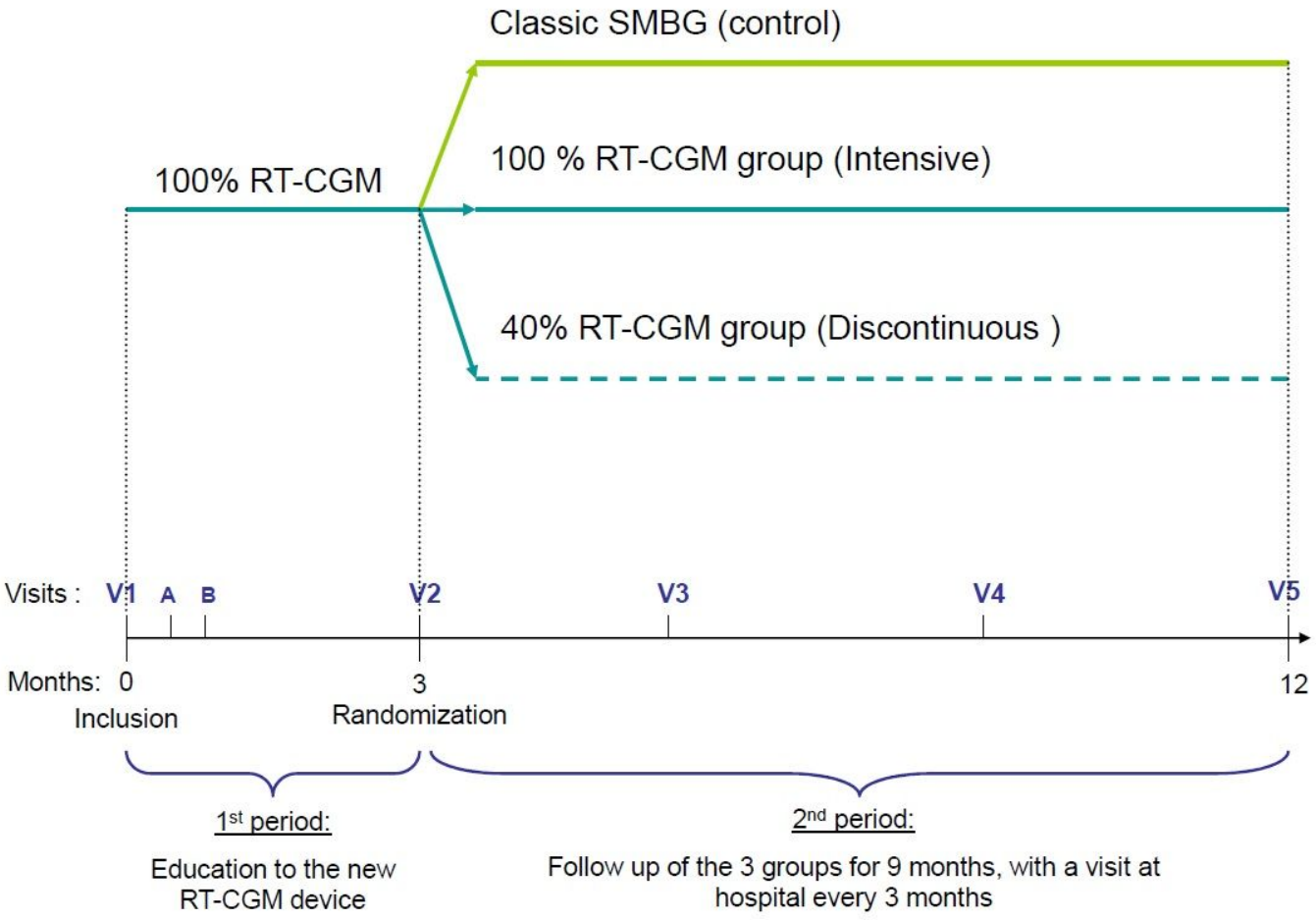

Figure 1

Design of the Start-In! trial. SMBG: self-monitoring blood glucose. RT – CGM: real-time continuous glucose monitoring. Discontinuous group: intermittent RT-CGM alternating with SMBG.

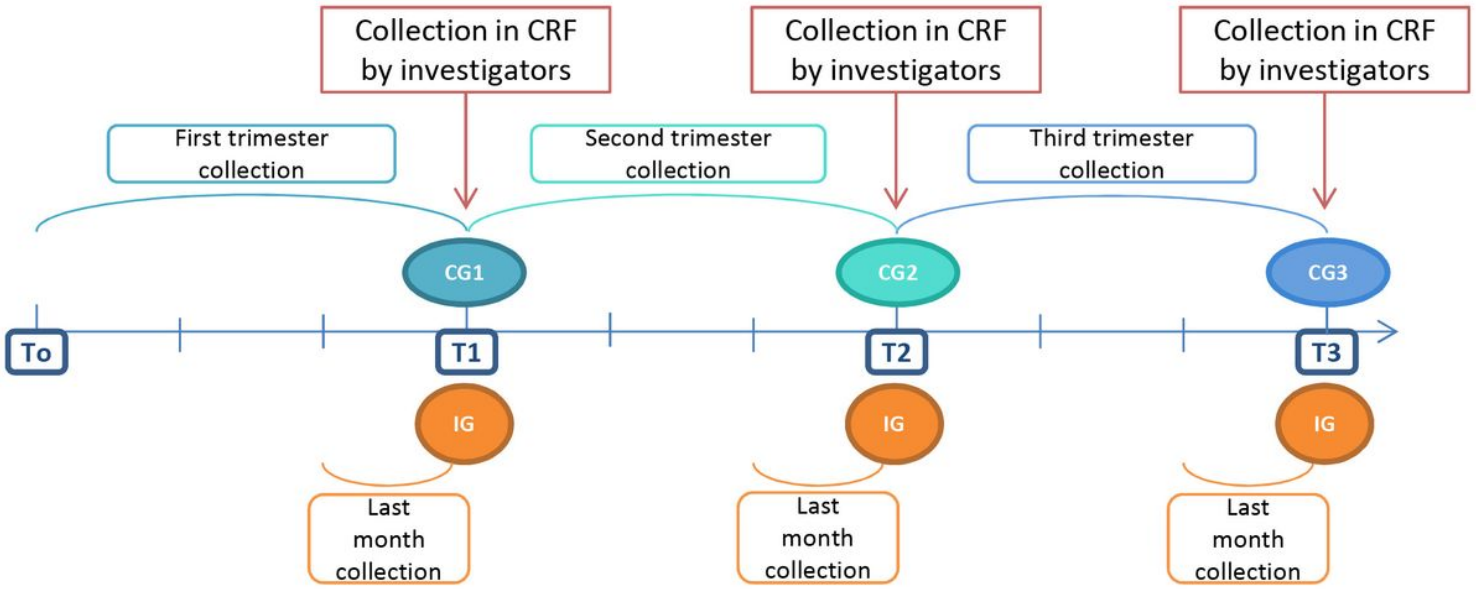

Figure 2

Timeline of the diary data collection for each randomization group, with T0 being the end of the third month of Start-In!. Blue ovals represent the continuous groups (CG1, CG2 and CG3) and orange circles represent the intermittent group (IG).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- LeJeannicSTROBEchecklist.docx