

Building clinical trials around patients: Evaluation and comparison of decentralized and conventional site models in patients with low back pain



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ABSTRACT

Clinical trials are slow and costly, built around the research centers that study local participants. Building clinical trials around patients in their homes and community through remote visits and monitoring could enhance recruitment and increase convenience for participants. This study evaluated different trial settings, a decentralized arm via telemedicine center (virtual study conduct), a conventional arm via health clinic (onsite study conduct) and a mixed model arm. Acute low-back pain patients (20–65 years) were recruited to this non-interventional trial in Switzerland. The study consisted of a screening period and a 2-week data collection period using direct data capture (eSource), electronic informed consent form (eICF), electronic diary (eDiary) and wearable actigraphy sensor.

A higher number of patients were enrolled in the decentralized arm (N = 18) compared to the conventional arm (N = 5) and none in the mixed model arm. The decentralized arm consisted of a diverse population with increased participation from rural areas. In the decentralized arm 89% of enrolled patients completed the study compared to 60% in the conventional arm. All the patients reported satisfaction with the use of eICF, eDiary and remote visits; whereas patients reported a lower level of satisfaction with the wearable sensor.

The decentralized setting was operationally feasible and well accepted by patients. Faster recruitment and improved access to patients was observed in the decentralized arm. This study supports broader adoption of the decentralized model in clinical trials, though further investigations in larger interventional trials are needed to confirm the benefits from this patient-centric approach.

1. Introduction

Recruitment and retention continue to be key challenges in randomized clinical trials (RCTs); between 50% and 60% of RCTs do not meet their original recruitment targets, or face significant delays [1,2]. Over the past decade, the complexity of clinical trial design has significantly increased in terms of the number of distinct procedures and planned onsite visits per protocol [3]. This negatively impacts a potential participant's willingness to enrol in a trial as it places a greater demand on their time and further disrupts daily activities [4,5]. In a global survey, the majority of respondents cited the physical location of a center as a very important factor in their decision to join a research study [6] and

reports show that the distance to a trial site is a barrier to participation [4,7]. Trends of increasing RCT complexity are moving counter to patient expectations of greater convenience of care [8,9].

This pilot study, a non-interventional trial in patients with acute low back pain in Switzerland using direct data capture (eSource), electronic informed consent form (eICF), electronic patient reported outcomes (ePRO) on electronic diary (eDiary) and wearable sensor was designed to compare decentralized, conventional and mixed model clinical trial settings. Low back pain patients were considered for this study as the prevalence of low back pain is rising and considered a major cause of disability that affects wellbeing [10]. The decentralized model evaluated has the potential to reduce barriers to participation and improve

Abbreviations: ERT, eResearchTechnology; eDiary, electronic diary; eICF, electronic Informed Consent Form; ePRO, electronic patient reported outcomes; RCTs, randomized clinical trials; RMDQ, Roland-Morris Disability Questionnaire; VAS, Visual Analogue Scale

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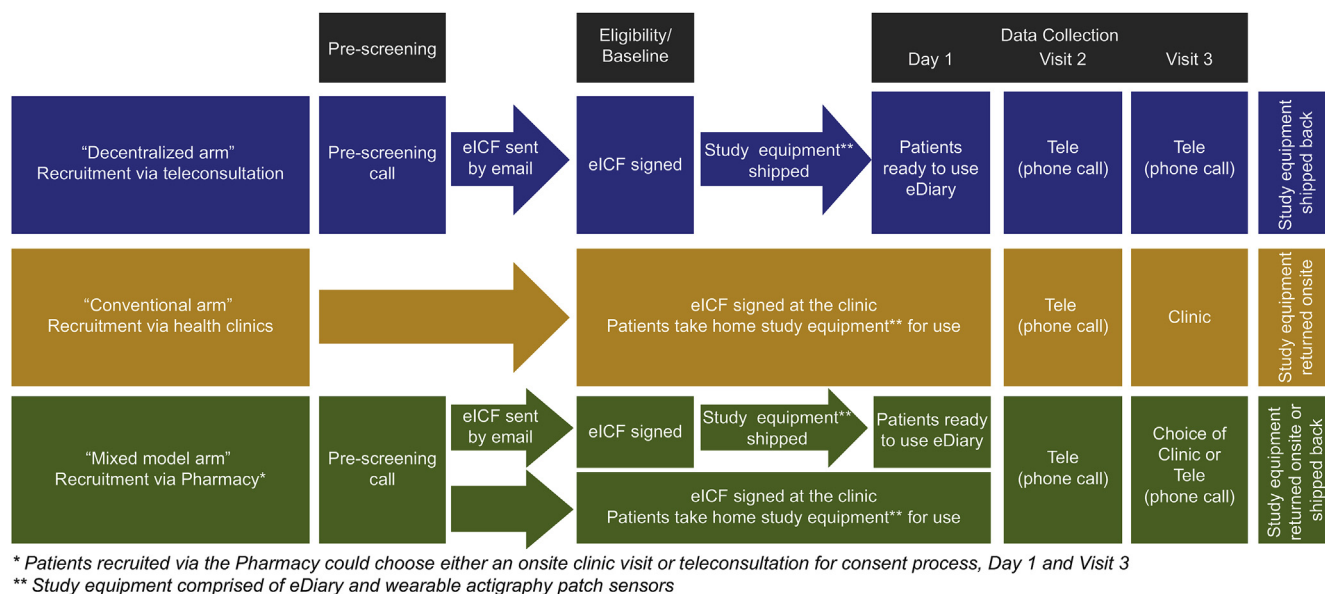


Fig. 1. Visit flow per arm.

retention by shifting the trial experience from a site-centric to a more patient-centric approach. The decentralized site model hinges on a single pivotal site managing patients within their usual environment by leveraging telemedicine, technology and local care providers. A growing body of evidence shows that telemedicine in combination with new technology, such as smartphones and wearable sensors, expand access and improve the patients' clinical trial experience by facilitating virtual clinical visits and remote monitoring [11–15].

From a Patient's perspective, as there are no or limited onsite visits required in the decentralized setting, impact on daily routine is minimized and geographical barriers to participation are reduced or eliminated. In a conventional clinical trial setting, sites tend to be clustered in urban areas [16,17]. Whereas with decentralization, trials can expand their reach to patients with poor access to healthcare such as those living in rural areas or with limited mobility [13]. These populations are typically underrepresented in research and the decentralized site model would allow a greater number of patients to have access to new innovative medicines. From a Sponsor's perspective, with reduced transportation barriers and increased convenience of participation, the rate of recruitment is expected to be faster in the decentralized than the conventional site model. Furthermore, the provision of a convenient trial experience may improve patient retention, compliance and enhance adherence to protocol requirements. In addition, decentralization could make clinical trial conduct more efficient by decreasing the overall number of sites needed to meet recruitment targets and minimizing the overall trial duration from protocol authorization to final report; thereby patients achieve faster access to new treatments [18,19].

2. Methods

2.1. Study design, participants, and objectives

This was a non-interventional study with the objective of comparing decentralized, conventional and mixed models for conducting a clinical trial. No therapy protocol was imposed and the low back pain patients were treated according to routine medical practice in Switzerland. The three models explored were a decentralized setting where all study visits and the consent process were conducted remotely via teleconsultation, a conventional setting where visits were conducted at the investigational site with the exception of one phone visit and a mixed model where patients could opt to follow the decentralized model, the

conventional model or a mixture of both. Additional objectives included (i) comparing the operational and recruitment methodology of the models (ii) assessing patient satisfaction with an eDiary and a sensor to monitor their pain level, physical activity and body posture, and (iii) evaluating patient compliance with reporting back pain medication use via an eDiary.

The study consisted of a pre-screening/baseline period and a 2-week data collection period. Eligible patients were adults between 20 and 65 years of age residing in Switzerland with a diagnosis of acute low back pain. Participants had to provide electronic informed consent prior to enrollment, be willing to complete the study related training and use the necessary study equipment throughout the duration of the study. Main exclusion criteria included any lack of cognitive capacity, inability to comprehend spoken or written English or German, inability to write in English or German and no or very limited access to the internet. This study was approved by the Swiss Ethics Committee of Basel (Ethikkommission Nordwest-und Zentralschweiz) and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines.

2.2. Participant recruitment and settings

Potential participants were recruited via the Medgate telemedicine center (decentralized arm), via treatment at the Medgate health clinic (conventional arm) or via Medgate partner pharmacies (mixed model arm).

As illustrated in Fig. 1, patients in the decentralized arm were recruited via teleconsultation and the study consisted of a pre-screening phase for potential participants to explain the study over the phone and release the eICF, further described in the subsequent section. The study equipment (eDiary and wearable actigraphy patch sensors) was shipped to the patients once their eligibility was assessed and the eICF was signed. Patients initiated the data collection (Day 1) following the receipt, training and set-up of the equipment. Patients were followed via a phone call at Visit 2 and Visit 3. On completion, participants returned the study equipment by shipping it back with provided return label.

In the conventional arm, potential participants were identified by their local physician. Patients interested in the study were provided with the eICF at the site. Eligible patients who consented were trained and provided with the study equipment at the clinic at Visit 1 and patients initiated the data collection (Day 1) the same day. Patients were then followed via a phone call at Visit 2 and attended an onsite

clinic visit for Visit 3. On completion, participants returned the study equipment at the last onsite clinic visit.

In the mixed model arm, potential participants were identified via purchases of medication for their low back pain at the pharmacy. Patients interested in the study would receive a follow up call and be given the choice whether to consent and perform Visit 1 at the site (same process as conventional arm) or remotely (same process as decentralized arm). Patients would have been followed via a phone call at Visit 2 and given the choice of an onsite clinic visit or a phone call for Visit 3.

2.3. Informed consent process

2.3.1. Decentralized arm

The Medgate telemedicine center staff identified potential participants when they called in for their acute low back pain. The center staff initially evaluated the potential participant's eligibility and confirmed their interest to learn more about the study. The patients who expressed interest were sent an email containing a link to access the eICF portal (remote consent) and they began the consent process by viewing and reading the form on their own internet enabled device. The telemedicine center scheduled a follow-up call with a study investigator in which patients could discuss any questions on the informed consent document, the trial or any concerns they might have prior to signing the consent form. Patients who consented signed the eICF electronically with their patient specific username and password and the form was then countersigned electronically by the study investigator or an authorized delegate. A hard copy of the signed eICF was included in the shipment of study equipment to the patient.

2.3.2. Conventional arm

Potential participants were identified through methodologies used in conventional trials. Patients at the Medgate health clinic who were interested in participating in the study received an email with a link to access the eICF portal via a tablet provided to them at the site. Patients were given time to read and understand the consent form and to discuss with the study investigator at the clinic any questions on the informed consent document, the trial or any concerns they might have prior to signing the consent form. Patients who consented signed the informed consent electronically with their patient specific username and password and the study investigator or designate countersigned electronically. Patients were provided with a hard copy of their signed eICF at the site visit.

2.3.3. Mixed model arm

Participants from the pharmacy that expressed interest in the study received a pre-screening call where they could choose whether to perform the consent process at an onsite clinic visit (same process as conventional arm) or via teleconsultation (same process as decentralized arm).

2.4. Data collection methods

The key components of the electronic data collection systems used in the study are outlined in Fig. 2 and were the same for all three models. The eResearchTechnology (ERT) portal was used as an eSource solution by site staff to record pertinent patient data and information on study activities. Access to the portal was restricted to authorized personnel who were trained on the systems and access was tracked. Study participants were provided with an electronic Diary (ERT Handheld eDiary) and a wearable actigraphy patch sensor (VitalPatch™ from VitalConnect) for use during the 2 week data collection period. The eDiary was provided on a Smartphone and the data collected was securely transmitted to a central database. The patch sensor provided was a disposable adhesive patch sensor (size 115 × 40 × 7 mm) with battery life of about 4 days, worn on the chest which enabled continuous,

remote monitoring of physiological activity data, including step count and posture (body position was derived from data collected when walking, running, standing, sitting and lying). Data from the patch sensor was transmitted wirelessly via Bluetooth to the eDiary when the devices were within range (3–10 m) of each other. Patients were trained by viewing a brief interactive training video on how to use and enter data on the eDiary as well as how to use, replace and connect the patch sensor to the eDiary. The patient training included a mandatory quiz as the first activity on the eDiary to ensure understanding of the devices and all patients had access to a patient guide as well as over the phone support, if needed. The patient's data transmitted from the eDiary was regularly reviewed and monitored by the site staff on the ERT portal throughout the study. To assist the sites with the remote monitoring of patients, an email notification was sent to site staff when no data was received at the central database from the eDiary for 72 h. Notifications were followed up via a phone call or other means previously agreed upon with the patient.

2.4.1. Data collected

A limited amount of data was collected for the study as the primary objective was to compare the decentralized and conventional site models. The data collected, timing of completion and tool used are outlined in Table 1. The site staff recorded information on demographics, baseline characteristics, recruitment methodology and study duration (from final signed ICF to end of study) on the ERT portal. Patients reported on a daily basis directly into their eDiary, their worst level of lower back pain during the last 24 h on a Visual Analogue Scale (VAS) and their daily pain medication use. In addition, on a weekly basis also on their eDiary, patients completed an ePRO, the Roland-Morris Disability Questionnaire (RMDQ). At the end of the study, patients were asked to complete a satisfaction survey available on the eDiary. The compliance (C) with use of the eDiary was assessed based on the number of daily diaries received (Dr) divided by the expected number of daily diaries (De); $(Dr/De) \times 100 = C\%$.

2.4.2. Data analysis

Demographics, baseline characteristics, patient disposition, patient's satisfaction, study duration, eDiary use, and compliance were summarized by descriptive statistics and/or frequency distributions.

3. Results

3.1. Patient recruitment and baseline characteristics

A total of 318 potential participants with low back pain were identified for the study, of which 180 were identified from consulting the telemedicine center, 18 patients from visiting the health clinic and 120 from purchasing low back pain medication at the pharmacy. The option to participate in the trial was not systematically presented to potential participants identified via the pharmacy and often it was not the patients themselves purchasing the medication. No patients were recruited in this mixed model arm. Out of the identified patients, 43 patients in the decentralized arm and 6 patients in the conventional arm fulfilled the criteria for the study. Of the 43 patients eligible in the decentralized arm, 18 patients enrolled and 25 patients decided not to participate in the study (13 were not interested after the pre-screen phone call and 12 declined to sign the eICF). Of the 8 patients eligible in the conventional arm, 5 patients enrolled. Both arms had the same duration for recruitment of 4 months, during which a higher recruitment rate was observed in the decentralized arm; 4.5 patients per month in the decentralized arm versus 1.25 patients per month in the conventional arm recruited (Table 2). The telemedicine center was able to recruit patients from 10 of the 17 German speaking Cantons, in contrast, the health clinic reached patients in 2 of these Cantons. Out of the 23 patients that enrolled in the study, 19 completed the study while 2 patients in each arm discontinued the study prematurely. The main

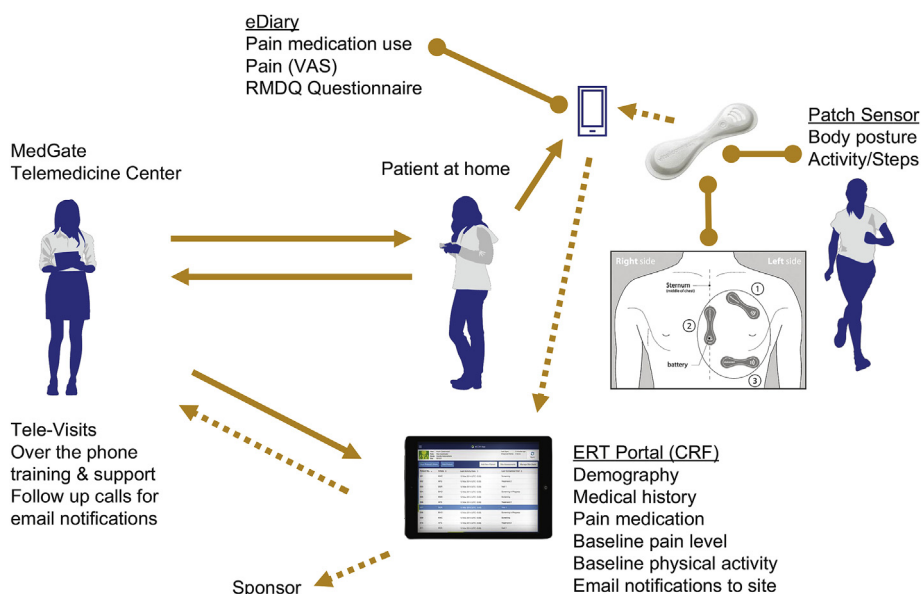


Fig. 2. Electronic data collection.

reasons for discontinuation were technical issues (2 patients) and lack of time/contact issues (2 patients). The overall mean age for enrolled patients was 38.3 ± 9.1 years with a range of 24–62 years and a wider recruitment across the different Cantons was observed in the decentralized arm (Table 3).

3.2. Operational aspects of the study (from signed ICF to end of study)

The total mean number of days in the study was approximately 21 days in the decentralized arm and 15 days in the conventional arm (Table 4). The reasons identified for this extended study duration in the decentralized arm were: a delayed start due to late retrieval of the study equipment shipment or multiple attempts were needed to schedule the last visit. A total of 9 patients required additional phone calls for technical issues in the decentralized arm and none in the conventional arm during the study.

3.3. Compliance and use of the eDiary

The mean number of eDiary days recorded was approximately 9 in the decentralized arm and 12 in the conventional arm (Table 5). The eDiary compliance level in the two groups was variable with a mean compliance of 63.0% in the decentralized arm and 83.4% in the

Table 2 Participant disposition.

Recruitment Parameters	Conventional arm	Decentralized arm	Mixed Model arm
Patients identified ^a (N)	18	180	120
Patients qualified (N)	6	43	0
Patients enrolled - signed eICF (N)	5	18	0
Patients completed (N)	3	16	0
Patients discontinued early (N)	2	2	0
Enrolled patients completing study (%)	60	89	N/A
Recruitment Rate (average number of patients per month)	1.25	4.5	N/A

eICF: electronic Informed Consent Form; SD: Standard Deviation.

^a Patients calling in via telemedicine center, patients coming in to the conventional health clinic or patients purchasing medication for lower back pain at community pharmacy.

Table 1 Data collected and tools used.

Tools	Parameters recorded in the tool	Frequency of Data Collection	Completed by Patient or Site Staff
eDiary (ERT smartphone)	Daily Diary: pain level on a VAS scale and daily pain medication use RMDQ questionnaire Patient satisfaction survey	Daily in the afternoon or evening between 15:00 and 22:00 for 14 days Weekly (Day 1, Day 7 and Day 14) Completed once at the end of the study	Patient
Patch Sensor (VitalPatch)	Physical activity (steps) and body posture (sitting, standing, laying).	Patch to be worn continuously, data transmitted automatically	Patient
Interactive training course on eDiary ERT portal	Interactive video course about the main steps during the study and how to use the eDiary and the patch sensor eSource (for case report form): ● Patient's age, gender, location ● Working situation and sick leave ● Baseline pain and physical activity ● Reports of all data collected, including eDiary compliance rates	Mandatory training quiz to be completed on the eDiary at the start of the study Scheduled study visits	Patient Site Staff

ERT: eResearchTechnology; RMDQ: Roland-Morris Disability Questionnaire; VAS: Visual Analogue Scale.

Table 3
Patient baseline characteristics.

Parameters	Conventional arm (N = 5)	Decentralized arm (N = 18)
Age (Mean, SD)	35 (11.1)	40 (8.2)
Gender (N)		
Female	1	8
Male	4	10
Patients working (N)		
Yes	5	17
No	0	1
Patients on sick leave at study entry (N)	0	5
Patients locations (N)		
City	4	8
Small village	1	5
Rural area	0	5
Number of Cantons Represented	2	10

SD: Standard Deviation.

Table 4
Operational aspects.

Parameters	Conventional arm (N = 3)	Decentralized arm (N = 16)
Total days in study ^a (Mean, SD)	15.0 (0.0)	21.2 (6.7)
Total contacts (phone calls, tele visits and/or onsite visits) per patient (Mean, SD)	3.0 (0.0)	4.3 (1.6)
Patients that needed additional phone calls ^b (N, %)	0 (0%)	9 (56.3%)
Patients that returned study equipment (N, %)	3 (100%)	13 (81.3%)

SD: Standard Deviation.

^a Total days from final signed ICF until Visit 3 (for one patient in conventional arm the date of deactivation in the ERT portal was used in lieu of Visit 3 date that was not available). For the decentralized arm this also included the time of the initial shipment of equipment.

^b Additional phone calls classified as unscheduled calls for technical issues or other support during the study.

Table 5
Compliance and use of eDiary.

Parameters	Conventional arm (N = 3)	Decentralized arm (N = 16)
eDiary Compliance ^a		
Ratio of daily diaries received to duration of data collection period (Mean, SD)	83.4% (8.7)	63.0% (33.3)
Patients with compliance rate of at least 80% on study completion (N, %)	2 (66.7%)	6 (37.5%)
eDiary use		
Average number of days with daily diaries recorded, (Mean, SD)	12.0 (2.0)	9.1 (5.2)

SD: Standard Deviation.

^a The ERT eDiary Compliance (C) is based on the number of daily diaries received (Dr) divided by the expected number of daily diaries, (De). $(Dr/De)*100 = C\%$.

conventional arm.

3.4. Use of the patch sensor

All the enrolled patients (N = 23) were provided with the patch

sensors. Three patients developed skin reactions and stopped wearing the patch sensor (2 in the decentralized arm and 1 in the conventional arm). Seven patients reported that the patch sensors did not adhere well (6 in the decentralized arm vs 1 in the conventional arm) leading to alternate ways of wearing them such as placing the patches in their pockets or on their back. Four patients reported incorrect data while using the patch sensor (3 in the decentralized arm vs 1 in the conventional arm). Additional patch sensors were sent to 5 patients due to battery or Bluetooth pairing issues (5 in the decentralized arm vs 1 in the conventional arm). Sensors were paired with eDiary on average every 2 and a half days (2 days, 13 h). There was high variability in the data obtained from the patch sensors due to the aforementioned reasons and hence no further analyses were carried out.

3.5. Patient's satisfaction survey

Patients were generally satisfied with the use of the eICF, eDiary and remote clinic visits; whereas a lower level of satisfaction was observed in the patients with the patch sensors (Fig. 3).

4. Discussion

The results of this pilot support the feasibility of adopting the decentralized site model and remote visits into broader clinical trials. As demonstrated in this study, patient enrollment into clinical research studies can be enhanced by removing the need for onsite visits and by using technologies which are patient-centric in nature. Acknowledging the small sample size, particularly in the conventional arm, a number of insights were gained into the conduct of trials in a decentralized setting through the evaluation of individual trial components used in the pilot study (such as method of participant recruitment, remote eICF process, remote patient training, shipment of study equipment and remote data collection). These learnings can be applied to trials considering an entirely remote study model or reducing the number of onsite visits with remote visits.

As expected in the decentralized model, the pilot confirmed a widespread recruitment of patients across the German speaking regions of Switzerland in the decentralized arm versus the conventional arm. The decentralized approach enabled outreach into rural areas as observed by the recruitment of one third of the patients from a rural location. In addition, the results show that decentralization fosters recruitment of diverse potential participants irrespective of geographical constraints. One of the key findings was the three times greater rate of recruitment observed in the decentralized arm compared to the conventional arm. In addition, a higher retention of enrolled patients was observed in the decentralized arm compared to the conventional arm with 60% of patients completing in the conventional arm and 89% of patients completing the study in the decentralized arm. The observed recruitment and retention rates are encouraging indications of the decentralized site model's potential to overcome these challenges in interventional trials. No patients were enrolled through the mixed model pharmacy arm due to the late involvement of the community pharmacy in study planning and the pharmacists cited lack of time and training as challenges to their participation. The pharmacy team proposed that this method of recruitment would be better suited to chronic indications where there is an established rapport with the patients as opposed to an acute medical condition such as low back pain. Though this study did not recruit patients through the mixed model pharmacy arm, this method of recruitment warrants further investigation and should not be discounted as other studies have successfully enrolled patients in community pharmacies [20–22].

The teleconsultation visits were well received by the patients in both the decentralized and conventional settings, especially when an effort was made to arrange calls outside the participant's working hours. Teleconsultation increases convenience for patients by reducing the time required for study visits which was cited by trial participants in

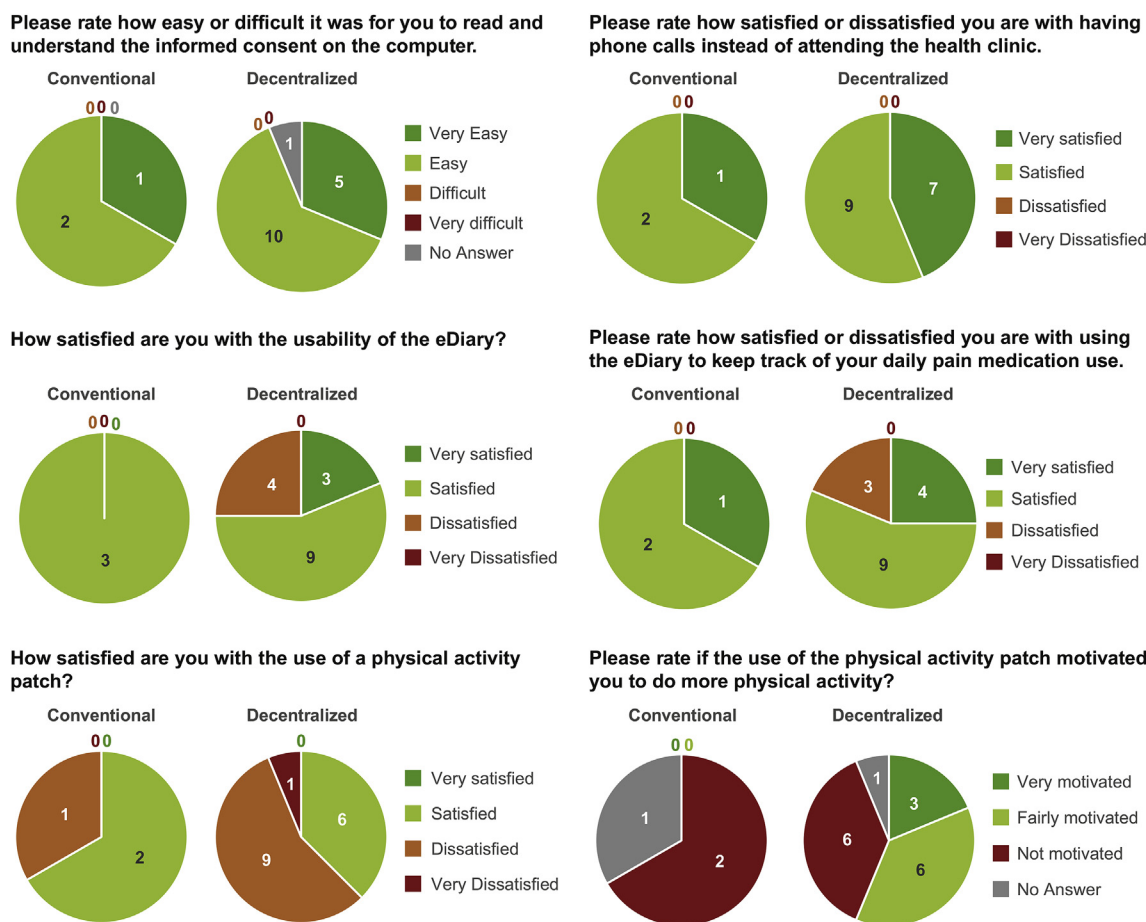


Fig. 3. Patient satisfaction survey results.

other studies as one of the aspects they least appreciated while taking part in a research study [23]. In a Parkinson's disease trial, teleconsultations represented a median saving of 88 min time compared to in-person care [24]. Although no patients were recruited to the mixed model setting, the possible advantages of this method cannot be disregarded, as the decreased number of onsite visits could reduce burden on site staff which could encourage site participation or increase their capacity to recruit patients [25]. As such, a mixed model leveraging teleconsultation and remote patient monitoring to reduce the number of onsite visits could enable conventional sites to enroll a greater number of patients with the same level of resources.

The technology used to enable the conduct of the study in a decentralized setting was well accepted by patients. In particular, the remote consent process using an eICF portal was perceived as easy to understand by all the patients and was approved for use in the study by the Swiss Ethics Committee. Patients in the decentralized arm were able to successfully set-up and complete the training on the study equipment remotely. Additional support was required for the majority of the patients in the decentralized arm, which was not unexpected and should be taken into account when using patient devices in this model. The limited number of patients included in both arms presents a challenge to the interpretation of the eDiary compliance data. Future studies would need to further investigate these aspects with a larger sample size and a longer data collection period.

The transfer of the data between the patch sensor and the eDiary did not function as intended for either study arm and was not related to the site model used. While this did not impact the overall outcome of the study as the objectives were not linked to the data obtained from the patch sensor; patients reported that their dissatisfaction with the sensor impacted their willingness to use the eDiary. There may have been a

knock-on effect where dissatisfaction with one technology component adversely impacted the use of the other. The VitalPatch sensor from Vital Connect was a newly released product which had not previously been used in conjunction with an eDiary from ERT. Hence, while using novel sensors a higher level of user acceptance and convenience of use need to be established to ensure that the multiple devices in the same study work together seamlessly. Sensors such as the one used in this study could add value by enabling the continuous remote monitoring of patients' activities and enhance prompt follow up by sites in case of significant changes to their status [11,26–28].

Beyond the technological components, a number of operational considerations would need to be taken into account when implementing a decentralized model. In this pilot trial, the average duration from final signed ICF until last contact was longer in the decentralized arm compared to the conventional setting. The main reason for this increase in duration was attributed to the logistics of device shipments where some of the patients took several days to retrieve the shipment from their local post office. In future trials, this could be improved by using a courier service where delivery can be scheduled at the recipient's convenience, for example, evening deliveries after business hours. However, given the increased speed of recruitment in the decentralized arm, this could still represent an overall reduction in trial timelines which would benefit the overall study conduct. A similar delivery approach may be used for study drugs along with study equipment in interventional trials. In addition, any instructions with regards to study drug given over the phone could be complemented with readily accessible informational videos on the eDiary. Although the study shows that the decentralized setting is feasible and advantageous, the small sample size, short duration of study conduct, single-country participation and non-interventional nature of the study limit the applicability

and reliability of the study results in a general manner on a broader interventional study. Further investigation and analysis would be needed to assess the extent of benefits in incorporating this model with respect to enhanced patient-centric approach, effective and economical clinical trial conduct along with faster access to novel treatments.

This pilot study showed that designing clinical trials in a patient-centric manner using a decentralized study setting is operationally feasible and well-accepted by the patients. The removal of geographical barriers to participation resulted in faster recruitment and improved access to patients living in rural locations. The findings of this pilot when considered together with the literature supporting technologies such as eICF, ePRO and telemedicine as well as information published on trials conducted remotely demonstrate that the decentralized site model is a functional buildup of the evolution of trends seen in clinical trials today.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.conctc.2018.06.008>.

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